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FLUOROSCOPY IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS[1]

L. HENRY GARLAND[2]

Fluoroscopic examination is a simple and convenient method of examining the thorax and reasonably accurate, provided the examiner becomes adequately accommodated and knows how to interpret the shadows seen on the fluoroscent screen. The method, however, has numerous disadvantages: it does not permit the detection of small infiltrates and cavities, it provides no permanent record (which could be checked by others or used for subsequent comparison) and, when large groups are examined, it may expose the physician to hazardous amounts of scattered radiation. In the following article the author will discuss the relative accuracy of fluoroscopy, some present day economics in radiographic examination of the thorax and will outline what he regards as the proper rôle of fluoroscopy in the diagnosis of pulmonary tuberculosis.

It is agreed that minute but clinically significant infiltration may be missed by roentgenograms, especially when plain or single films are used. It is likewise agreed that the roentgenogram is not a delicate test for the presence of active minimal tuberculosis. However, it is the most efficient, readily available test for the detection of clinically significant lung infection which we have to-day.

The efficiency of a fluoroscopic unit varies moderately with the technical factors, and greatly with the time taken to get the eyes adapted. Most fluoroscopes are operated at from 65 to 85 KV. and from 2 to 10 MA. With a modern Patterson B screen, and a thin scatter-diminishing grid (of the Lysholm type), we believe that about 75 KV. and 5 MA. are satisfactory factors. If the target-skin distance is 18 inches and a thin aluminum filter is used, the patient's skin gets from 8 to 18 r per minute (as measured by the author on different installations). Inefficient fluoroscopes give as low as 4 r per minute, and modern enclosed fluoro-

[1] Read by invitation at the annual meeting of the California Trudeau Society, Del Monte, California, April, 1941.

[2] 450 Sutter Street, San Francisco, California.

scopes (in which the tube-top distance is usually only 14 inches) about 30 r per minute. I have seen one internist use 20 MA. at a short distance, routinely; it is probable that his patients were getting about 50 r per minute—an unhealthy dose both for patient and physician. Another physician read his milliameter on the wrong scale and used 50 instead of 5 MA. as long as the tube lasted. He considered his fluoroscope very superior; it was, especially in skin effect.

There have been too many cases of damaged skin to regard the fluoroscope as a harmless weapon. However, it is the scattered radiation which most of us should beware of, and this can best be diminished by using small beams and working fast. Conventional lead aprons and gloves are of little use in chest work.

THE ACCURACY OF FLUOROSCOPY

There have been several groups of studies on the relative merits of fluoroscopy and roentgenography in the detection of pulmonary tuberculosis, the majority establishing the fact that fluoroscopy is considerably less accurate than radiography, even when carefully conducted by persons trained and experienced in both methods. The reasons for this inaccuracy have been discussed by many authors and depend largely on the fact that conditions offered the human eye in the two instances are decidedly different. The visibility of an object depends on its absolute and relative brightness and on the angle of vision at which it is seen. The brightness of fluoroscopic shadows is so enormously less than that of radiographic shadows that the retina is unable clearly to distinguish small differences in contrast, such as are produced by small infiltrates and cavities. The ability of different persons to see clearly in dim light varies considerably and this fact alone appears to account for a considerable proportion of the errors resulting from fluoroscopy. The following is a summary of the more important published studies on the problem. The percentages given are taken from the authors' published data, *not* from their own summaries, since most of them favor the method and give figures based on all cases examined, not on all diseased cases found (see especially Israel and Hetherington's article).

Hetherington and Flahiff (6) studied 347 students (ages sixteen to twenty-five years) both by fluoroscopy and stereoscopic roentgenograms. Of 294 cases interpreted as negative by fluoroscopy, 31 showed positive radiographic findings ("apical tuberculous infiltrate or pulmonary nodule"), an error of over 10 per cent. Of 17 cases reported

positive for apical tuberculous infiltrate by fluoroscopy, 6 were negative by radiography, an error of over 35 per cent. They concluded that by fluoroscopy they missed several small supraclavicular apical lesions, and misinterpreted as apical lesions areas of diminished aeration (caused by one shoulder being lower than the other or the ribs on one side being closer together).

Reid (10) studied 1,035 supposedly healthy persons both by fluoroscopy and roentgenography. In the entire group she detected 10 cases of pulmonary tuberculosis, but missed 2 of them by fluoroscopy (an error of 20 per cent). She concluded that the best means of detecting pulmonary tuberculosis is by the use of stereoscopic roentgenograms, but that fluoroscopic examination is approximately as accurate as the plain film!

Fellows and Ordway (5) compared the fluoroscopic and roentgenographic findings of 2,300 persons and concluded that they had an error of 13 per cent—that is, 13 per cent of clinically significant tuberculous lesions were missed by fluoroscopy, even though the latter was done under the best possible conditions.

Voigtlander (13) studied a similar group of cases and noted that in 32 per cent incorrect or insufficient diagnoses were made by fluoroscopic examination alone. He commented "professional roentgenologists are exposed daily to the limitations of fluoroscopic examination and need no such statistical data to prove its limitations."

Schaare (11) studied 400 cases by fluoroscopic examination and roentgenograms and found an 18 per cent error by fluoroscopy.

Chantraine and Cramer (3) tested the ability of a group of 30 physicians to see in the dark, employing lead numbers of various sizes and a standard fluoroscope. Six physicians, or 20 per cent, were classified as having good ability, 10 as medium and 14 as poor. Two-thirds of the group needed at least ten minutes for adequate adaptation to read all numbers. They concluded that it would be advisable to test in the dark the visual acumen of physicians who are supposed to do chest fluoroscopy, especially when fluoroscopy is used as the only method of roentgen examination.

Licht (9) made a series of careful photometric tests under various conditions of fluoroscopy and radiography. By means of visual-power curves and power-of-distinction curves he showed that the reduced illumination in fluoroscopy diminished the capacity of the eye to distinguish both contrast and form. The detail is actually on the fluoroscopic screen, but the brightness and contrast of the shadows are so weak that they cannot always be appreciated by the retina. He stated that

the current could be increased to produce a degree of brightness adequate for diagnosis, but that this would involve a skin dose of about 100 R. per minute (in contrast to the ordinary roentgenographic skin dose of 0.3 R. per exposure). In his clinical work he found an absolute error of 25 per cent with fluoroscopy as compared with radiography; however, if he eliminated all of the negative cases in both groups, the total error by fluoroscopy rose to 65 per cent. He believes that if fluoroscopy is done by a skilled observer with good dark vision, and if roentgenography is performed on all suspected cases, including individuals whose adiposity makes it impossible to see good detail by fluoroscopy, the method is a satisfactory one for survey purposes. But he regards fluoroscopy alone as a crude method in the examination of individual cases for pulmonary disease.

Israel and Hetherington (8) analyzed the results in a group of 973 cases subjected to fluoroscopic and radiographic examination. The fluoroscopic examination was done by 18 different physicians, some with special training in roentgenology and some without. Attempts were made to reach definite conclusions from the fluoroscopic examinations, but one notes that the adjectives "probable" and "unlikely" qualify many of the reports. The authors concluded that "fluoroscopic examination in diagnostic practice or in mass surveys should detect almost all tuberculous infiltrations of clinical significance," and state that in the present series of "approximately 1000 duplicate examinations in only four instances were significant lesions not recognized." However, if one analyzes their data one discovers that the percentage error is much higher than these figures suggest. They report 211 clinically significant lesions in the entire group and state that 4 of these were missed by fluoroscopy (an error of approximately 2 per cent). Over one-half of these clinically significant lesions were far advanced cases and indeed the percentage of active tuberculosis lesions in the entire group was approximately 20 per cent, indicating the highly selected nature of the material studied. (It is to be remembered that in most studies of this type the incidence of clinically significant tuberculous lesions is usually less than 2 per cent). The authors believe that they missed only 2 per cent of the moderately advanced lesions and about 6 per cent of minimal lesions. However, in 281 cases in which a fluoroscopic diagnosis of positive or probable disease was made, the roentgenograms were confirmatory in only 247, revealing an error of approximately 12 per cent. They confirmed the opinion of other workers in regard to the marked variability

of visual acuity of individual physicians in this type of work, but found no explanation for this in refraction studies, vitamin-A determinations and so forth. They believe that small supraclavicular lesions are frequently overlooked, but that failure to detect gross lesions is usually due to inadequate dark adaptation.

There have been several studies published of the results of large groups of fluoroscopic examinations, in which only cases with positive fluoroscopic findings were subjected to subsequent roentgenography. Some of these studies (such as that of Chalek and Bergh (2)) demonstrate a tendency of persons doing surveys to stray away from the main problem, namely, the detection of active, and especially open, cases of pulmonary tuberculosis. In these studies a high percentage of pulmonary lesions is reported, but when the lesions are analyzed it is found that the majority of them consist of clinically insignificant conditions such as small calcified foci, areas of apical pleural thickening, so-called hilar enlargement and so-called cardiac enlargement. The incidence of active or open pulmonary lesions, as checked by subsequent clinical and sputum examinations, is frequently omitted in the reports of the studies. There is a great tendency to exaggerate the significance of normal bronchovascular markings, of normal hilar markings and to overestimate the size of the heart and aorta. However, nearly all authors conclude by admitting that the fluoroscopic method is considerably less accurate than the radiographic.

Stiehm (12) is the most optimistic of the protagonists of fluoroscopy alone. He reported 4 cases of minimal pulmonary tuberculosis "not visible on the plain film but visible at fluoroscopy." Now it is conceded that such an eventuality is possible, but the 4 cases he cites do not substantiate the thesis. His protocols show that there was an interval of several weeks between roentgenography and fluoroscopy in each instance! The initial (and negative) films were made respectively three, four and a half, three and two weeks before fluoroscopy. When roentgenograms were made immediately after fluoroscopy the discrepancy disappeared (and the roentgenograms were invariably more complete). It is well known that pulmonary infiltrates and nodular foci may show considerable change in a period of less than two weeks, especially when active inflammatory or allergic changes are present. Therefore Stiehm's cases cannot be regarded as proof that fluoroscopy is superior to roentgenography in this matter.

Stiehm's "method for fluoroscopic examination" bears noting inasmuch as he is much quoted by the proponents of diagnostic fluoroscopy:

"Having determined that the individual is not too largely proportioned to permit a satisfactory fluoroscopic examination, it is important that a definite routine be followed. The examiner should accommodate his eyes by wearing goggles before entering the fluoroscopic room, and *at all times* therefore when entering a lighted room. He should arrange his schedule so he may examine a specified group without often emerging from the fluoroscopic room. The subject is examined with the clothing removed to the waist, facing the fluoroscope, with the shoulders rotated forward, thus keeping the scapulae out of the field of vision. The entire thorax is first surveyed, noting any asymmetry. The neck is examined for calcified cervical lymph nodes. Any abnormality of the bony framework is noted, such as the presence of cervical ribs, and structural defects of the ribs and spine. The movement of the ribs and diaphragm is then observed, search especially being made for localized limitation of motion, presence of adhesions and the obliteration of the costophrenic angles. The heart, aorta, mediastinum, and retrocardiac space are next examined in the posteroanterior, anteroposterior, right and left oblique, and lateral views; and abnormalities noted. The hilum is then studied and the extent of its outer boundary noted. It should not normally extend beyond the inner third of the pulmonic field. Examination of the hila is probably the most unsatisfactory part of the examination, for though the hilum may appear 'muddy' in certain parts, the density noted may not be sharply enough defined or sufficient enough in detail to tell definitely that it represents a calcified deposit. Distinction between blood vessels on-end and calcifications slightly removed from the hilum is readily and easily made by rotating the patient.

"Finally the lung fields are examined. With the shutters of the fluoroscope wide open a general survey of the lung is made. Any large infiltration is readily seen. With the shutter arranged to expose a three-inch strip of lung, homologous parts of the two lungs are compared by slowly turning the patient from side to side and slowly elevating the screen so that all parts of the lungs may successively be viewed. The apices, clavicular and subclavicular regions are closely inspected in all positions with the scapulae drawn both up and down, but always forward. Closer inspection of these important portions of the lung field should be done with the shutter of the diaphragm so regulated that only small parts of the lung can be successively examined. By inspiration and expiration the position of the ribs over the apices can be changed so that thickening of the apical pleura or subminimal infiltrations at the extreme apices can be brought into view. Frequently these are not visible on films unless several are taken in various phases of respiration.

"*The entire routine is repeated* while the patient faces the examiner. Since

most infiltrations are in the posterior part of the lung, they usually appear larger in this position."

Stiehm and others report they can perform at least thirty such examinations per hour!

Personal experiences with failures in fluoroscopy are familiar to most of you. However, the general public, medical and otherwise, still places too great reliance on the method as is evidenced by the two following cases.

Case 1: A middle-aged clergyman complained of indigestion and being easily fatigued. He had been attended by a well known internist who had fluoroscoped his chest and stomach on two occasions without finding anything abnormal. On the day of the last negative fluoroscopy the patient was referred to a radiologist for examination. Fluoroscopically, a little clouding was detected in the right upper lobe region but otherwise the lungs appeared clear; the diaphragm was normal. The gastro-intestinal tract appeared normal. Radiographic examination of the chest revealed extensive infiltration in the right upper lobe (figure 1). Sputum examination disclosed bacilli and the patient is now undergoing treatment for an active tuberculous lesion which in all probability could and should have been picked up radiographically several months previously.

Case 2: A young housewife consulted a physician on account of lower abdominal pain of one week's duration. She had been in a sanatorium five years previously with "rather extensive bilateral apical pulmonary disease without cavitation." She left the sanatorium after one year and was cared for by a chest specialist at his office, who fluoroscoped her repeatedly but made no further radiographic examinations over a period of four years! She left him to consult the first mentioned physician, who referred her for roentgen examination. This disclosed bilateral upper lobe disease, apparently active, with fibrotic changes in the middle third of the right lung and moderate pleural thickening (figure 2). The clinical diagnosis was (*a*) probable acute pelvic inflammatory disease and (*b*) active pulmonary tuberculosis. The patient was given pneumoperitoneum and bed-rest and improved gradually.

These cases have occurred within the last year and are a fair sample of what often happens with fluoroscopy under ordinary conditions of private practice. This fact must not be evaded: most of the chest fluoroscopy done to-day is being done by general practitioners or internists, who have had little or no instruction in the limitations of the method and who rarely take the time to become properly adapted. They give their patients a false sense of security, and overlook many cases of pulmonary tuberculosis at a stage when it is most curable.

FIG. 1

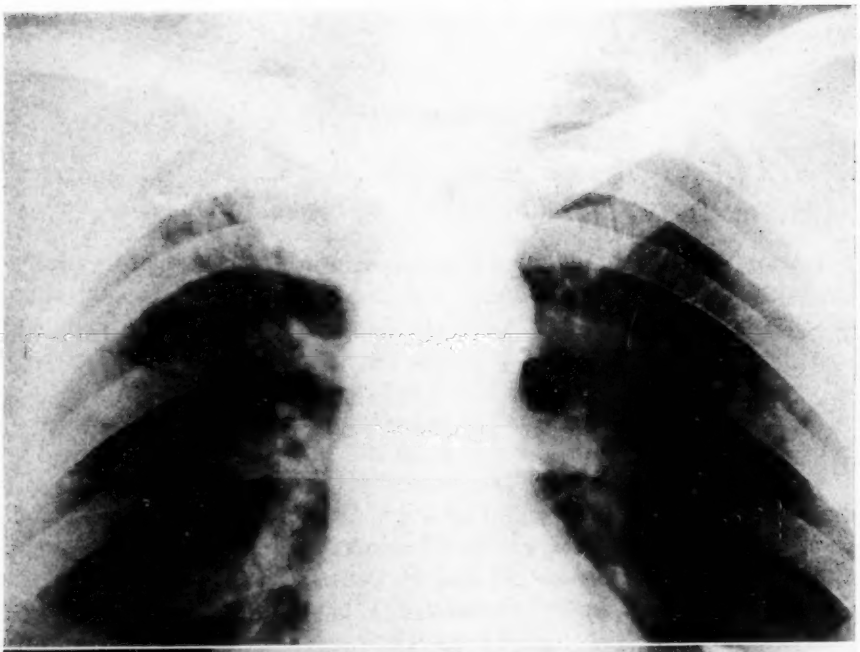

FIG. 2

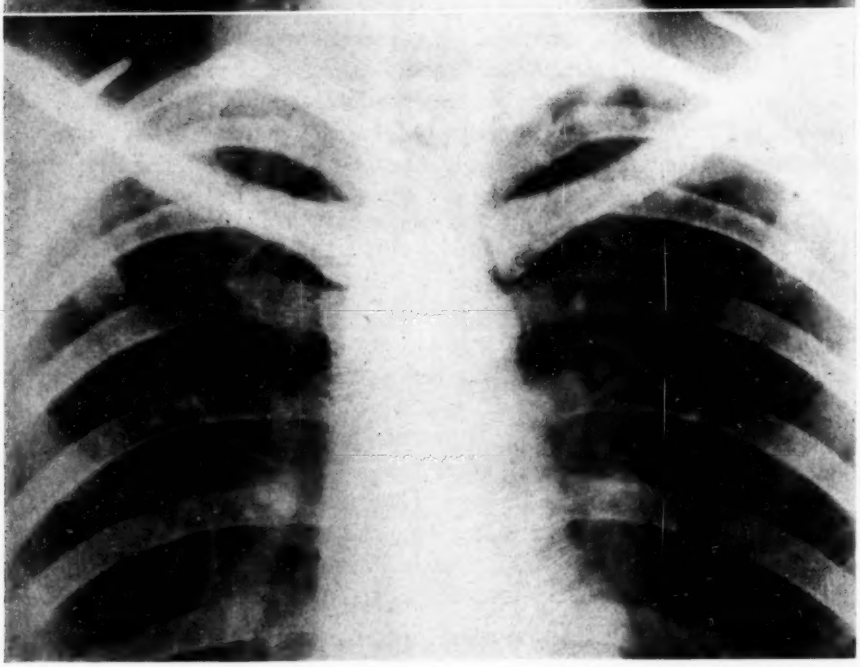

FIG. 1. Case 1. Roentgenogram of chest made on the same day as a negative fluoroscopic examination (as reported by the patient's physician, an internist). Note the extensive, soft, linear densities in the right upper lobe. Sputum positive for tubercle bacilli shortly thereafter. This active tuberculosis could, and should, have been detected by radiographic examination many months earlier.

FIG. 2. Case 2. Roentgenogram of chest made one week after a negative fluoroscopic examination (by the patient's former physician, a chest specialist). Note the nodular areas of increased density in both upper lobes: clinically, active pulmonary tuberculosis. This patient had been in a sanatorium five years previously, had discharged herself after one year, and been followed for four years by the chest specialist, during which time no films were made. She was returned to bed, given pneumoperitoneum and improved slowly. Serial fluoroscopic examinations must be checked at intervals with radiographic examinations to prevent the occurrence of cases like this.

It is quite proper that the physician has at his disposal any and all available diagnostic or therapeutic weapons, provided he understands how to use them. The use of the fluoroscope is analogous to that of the electrocardiograph: it may be highly informative or highly misleading. It impresses both patient and physician with a sense of accuracy and finality in diagnosis that can be quite harmful. The number of patients told they have cardiac disease after an EKG has been made by the average doctor probably exceeds that of tuberculous lesions missed by fluoroscopy in the same hands, but the increasing sale of small cheap fluoroscopes may well reverse matters. Unless the physician has had an *unusual* amount of training in a given complex, mechanical diagnostic procedure, he and his patients are better off if reliance is placed on sound clinical methods. If he has seen and been chagrined by the innumerable errors resulting from fluoroscopy alone, then he may be equipped to use the instrument to the benefit of his patients.

The director of tuberculosis of one large California institution (7) reports, "We have several films of patients who, a few months after being told they had nothing in their chests on fluoroscopy, had far advanced lesions when radiographed. Three of these cases are recent ones."

Bloch (1) observes, "We are aware that fluoroscopy has the disadvantage of not providing a permanent record and that it requires special training which not even the average chest specialist has. We have witnessed programs going on in which, on account of the inexperience of the examiners, the results were not as good as they might have been and many cases of tuberculosis were missed."

THE ECONOMICS OF FLUOROSCOPY VERSUS RADIOGRAPHY

It is difficult to determine the actual cost of performing professional procedures since there is no general agreement as to what the services of a physician are worth. However, there is general agreement that the approximate cost of making *individual* chest examinations by a roentgenologist in private practice varies from four to eight dollars depending on the volume of work and the type of examination performed. The examination takes only a few minutes of the physician's time (at preliminary fluoroscopy, informing the technician what projections to make, and studying and reporting the films when finished).[3] In certain cases

[3] The film cost is a relatively minor one, except when unusually large numbers have to be examined in a very short period of time. The overhead, including personnel, rental, depreciation and so forth, constitutes from 60 to 90 per cent of the cost. Therefore, the saving with miniature film in *private practice* may be as low as 15 per cent when computed by proper accounting methods.

a considerable amount of time is consumed in consultation with the family physician or relatives subsequent to the making of the examination. On the other hand, if one attempts to rely on fluoroscopy alone, the fluoroscopic examination takes a great deal of time. Private patients come to a roentgenologist's office or department more or less haphazardly; it is not possible to have them all come by appointment. If one is to fluoroscope individual cases, and get properly adapted before making the examination, the time consumed varies from twenty to thirty minutes. Subsequent to examination a report must be made, the case discussed with the attending physician, and so forth. If a physician's office time is valued at ten dollars an hour, it is obvious that an individual fluoroscopic examination represents approximately five dollars. The saving over radiography is therefore negligible.

On the other hand, in survey work where large groups of cases can be studied at one time, the relative cost of the two procedures is very different. Depending on whether the cases are surveyed in a physician's office or in a clinic, the cost of radiographic examination drops to between four and two dollars. The lower figure applies when rent, depreciation and so forth are ignored. In the San Francisco City and County Hospital the cost of making individual radiographic examinations of the thorax is about $3.50 per case. Mass radiographic examinations (especially on miniature film) cost less and mass fluoroscopic examinations still less. From 20 to 30 persons can be fluoroscoped per hour and the number of assistants need not be very great. However, to register, supervise the dressing room, place the patient and make the records, the time of from four to six persons can readily be used. The immediate cost of mass fluoroscopy in dollars may be one-tenth of what radiography is. However, the cost of caring for one missed case of tuberculosis may exceed that of complete radiographic examination of a given group, and there is a fair chance of missing one active case for every 5 active cases detected when reliance is placed on fluoroscopy alone! If a very large group of persons is surveyed by only one or two physicians, an additional problem must be reckoned with, namely, the potential damage to the physician's haemopoietic system by scattered radiation. The cost of this in dollars obviously cannot be estimated.

Edwards and Ehrlich (4) after reviewing mass surveys of over 100,000 individuals in New York state that in their opinion the advantages of fluoroscopy (low initial cost and upkeep) are outweighed by several disadvantages: "The accuracy of diagnosis is hampered by the human

element. The fluoroscopic interpretation represents the impression of a single individual that cannot be reviewed by others, and it does not leave a permanent record that can be compared with subsequent examinations. In mass surveys we have found the X-ray film to be more satisfactory regardless of the extra cost involved."

THE ROENTGEN DIAGNOSIS OF PULMONARY TUBERCULOSIS

Strictly speaking, the diagnosis of pulmonary tuberculosis cannot be made either by fluoroscopic or radiographic examination. An experienced radiologist can frequently arrive at a correct conclusion that a given series of shadows indicates an active lesion, and that the lesion is in all probability tuberculous. However, X-ray methods merely localize the lesion and indicate its probable nature; its true nature can only be determined by correlation of the X-ray findings with the clinical findings and especially with the results of sputum examination. The roentgen diagnosis of activity usually requires serial examinations. Individual X-ray examinations have the primary object of detecting any type of pulmonary, pleural or intrathoracic disease. Mass examinations have the primary object of detecting active and especially open lesions. A small, but not negligible, percentage of cases of active pulmonary tuberculosis, will be overlooked by any method of examination at present available, including bronchoscopy. The presence of an active lesion may be suspected as a result of suitable tuberculin tests, blood sedimentation rate and similar studies. However, as in every other type of medical procedure, a negative report never excludes a minute, active focus of disease at any given time.

The percentage of cases of active pulmonary tuberculosis found in routine X-ray surveys of adults varies widely, depending in part on the economic circumstances of the group and in part on the criteria by which the term active is defined. If by active we mean cases verified by subsequent radiographic and bacteriological examinations, the percentage in the ordinary population is quite small, perhaps 0.5 per cent. Of this small percentage not more than one-half, or 0.25 per cent, have open lesions.

THE PROPER RÔLE OF FLUOROSCOPY

The proper rôle of fluoroscopy in the diagnosis of pulmonary tuberculosis is that of an adjunct, an adjunct to radiographic examination which must be regarded as indispensable in individual cases. Fluoros-

copy is of value in determining the aerability of various portions of the lungs, especially those areas partly concealed by adjacent structures, the mobility of the diaphragms and mediastinum and the behavior of apparently encapsulated collections of fluid or air. It should be used in conjunction with properly made roentgenograms, stereoscopic postero-anterior films as well as lateral, oblique or other projections as indicated in the individual case. Wise interpretation of the fluoroscopic and roentgenographic findings completes the X-ray examination.

With fluoroscopic examination alone, small tuberculous infiltrates, especially in the apex, and small active lesions elsewhere in the lungs are easily overlooked. The existence of a significant tuberculous lesion cannot always be excluded by fluoroscopic examination, especially in thick-chested or fat individuals. The observer tends to attribute undue significance to normal bronchovascular markings and normal variations in cardiovascular shape and size. Bearing in mind these points and the importance of adequate adaptation, fluoroscopy can be of considerable service in mass examinations, being far superior to routine physical examination for the discovery of pulmonary disease. The official publication of the National Tuberculosis Association, 1940 Edition (Diagnostic Standards of Tuberculosis), sums the matter up concisely: "To detect the average minimal lesion of pulmonary tuberculosis X-ray films are indispensable, since there may be no abnormal physical signs. With fluoroscopy some ten to fifteen per cent of clinically significant minimal lesions will be missed. While a positive sputum makes the diagnosis certain, it is greatly to the patient's advantage if a diagnosis can be made and treatment instituted before a productive cough has developed or tubercle bacilli can be found."

The percentage error with fluoroscopy (as contrasted with roentgenography) in the diagnosis of significant pulmonary tuberculous lesions has been demonstrated to vary from 13 to 35 per cent even in the hands of experts. This fact must be borne in mind in order to avoid a false sense of security when relying on the fluoroscopic method alone. In experienced hands it is far superior to clinical examination, but considerably inferior to roentgenographic examination.

SUMMARY

The author reviews the rôle of fluoroscopy in the diagnosis of pulmonary tuberculosis. Using the published data and figures of even ardent protagonists of fluoroscopy, he shows that the relative accuracy

of this method is much lower than one might gather from the conclusions of these authors. He discusses the simple physical and psychological reasons for this loss of accuracy, and cites some personal experiences in support of his thesis, namely, that "fluoroscopy is not sufficiently accurate to be relied upon for the detection of active tuberculous lesions." He agrees that the method is much more accurate than simple physical examination, and is of great value for the detection of extensive or moderately advanced disease, especially when cavities are present. The percentage error of fluoroscopy as contrasted with roentgenography varies from 13 to 35 per cent even in the hands of experts. If this fact is borne in mind a false sense of security will be avoided when relying on the fluoroscopic method alone. Fluoroscopy in individual cases is essentially an *adjunct* to complete or proper roentgenographic examination; in mass surveys it is far superior to simple physical examination but not nearly as accurate as properly conducted roentgenographic examination.

SUMARIO

Repásase aquí el papel de la roentgenoscopía en el diagnóstico de la tuberculosis pulmonar. Tomando los datos y cifras publicados hasta por los defensores más ardientes de la roentgenoscopía, demuéstrase que la relativa exactitud de este método es mucho menor que la que podría deducirse de las conclusiones de dichos autores. Discútense las sencillas causas físicas y psicológicas de esta inexactitud, y cítanse algunas observaciones personales en apoyo de la tesis aquí defendida, a saber, que "la roentgenoscopía no es suficientemente exacta para atenerse a ella en el descubrimiento de las lesiones tubeculosas activas." Conviénese en que el método es mucho más exacto que el mero examen físico, y en que posee mucho valor para el descubrimiento de la enfermedad, ya extensa o moderadamente avanzada, sobre todo cuando existen cavernas. Comparada con la roentgenografía, los errores de la roentgenoscopía representan de 13 a 35 por ciento aun en manos de peritos. Teniendo esto presente, se evitará una falsa sensación de seguridad al atenerse exclusivamente a la roentgenoscopía. En casi todos los casos, la roentgenoscopía viene a ser sencillamente un auxiliar del completo o adecuado examen roentgenográfico; en los censos en gran escala resulta muy superior al mero examen físico, pero mucho menos exacta que un examen roentgenográfico debidamente ejecutado.

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ROENTGENOSCOPY OF THE LUNGS[1,2]

Its Adequacy as Determined by Spot Roentgenography

REUBEN H. STIEHM[3]

The decision regarding the adequacy of any method of examination is not decided by the experience of one, but of many examiners. It is this total experience that eventually determines its advantages and its limitations. To-day, few will deny that the X-ray examination of the lungs is the most efficient method of finding visible evidence of early tuberculosis. But even the X-ray film has its limitations! A lesion may not yet be large or dense enough to cast a shadow, or it may be hidden by the bony framework, or it may be at the extreme periphery of the lung and therefore not visible on the film taken in the routine posteroanterior or anteroposterior position. It may be dense enough in one plane to cast a shadow and not dense enough in another to do so.

That active tuberculosis exists without appearing on the roentgenogram is evidenced by the fact that tubercle bacilli (proved by guinea pig inoculation) have been found in the gastric contents of fasting individuals who have recently had pleurisy with effusion and in the gastric contents of children who have been exposed to a parent with active tuberculosis. We have on record one university student whose gastric contents were repeatedly positive by guinea pig inoculation for a period of twenty-seven months after an effusion occurred; this, without the development of a visible parenchymal lesion.

Another student, negative to 1 mg. of Old Tuberculin in December, 1940, developed a spontaneous pneumothorax on the left in April, 1941. Because his tuberculin test had become strongly positive, the fasting gastric contents were aspirated on three successive mornings and were found positive by guinea pig inoculation. Stereoscopic films taken in April, 1941 and June, 1941 were interpreted as showing no parenchymal change. Roentgenoscopy, however, which showed no visible lesion in

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[2] This work was made possible by grants from the National Tuberculosis Association and the Wisconsin Alumni Research Foundation.

[3] Dr. Reuben H. Stiehm died on October 21, 1941.

April, 1941, revealed the presence (figure 12) of a small infiltrate in the right lung in June, 1941. The fact that the spontaneous pneumothorax and the infiltrate occurred in opposite lungs may have been coincidental and leaves the aetiology of the pneumothorax in doubt.

The presence or development of a positive Mantoux reaction is the earliest and most delicate test now available to indicate that tubercle formation has occurred somewhere in the body. In a large majority of cases it is in the lungs. Since this is true, repeated X-ray examination should be primarily directed toward studying the lungs of the infected, especially those recently infected, to determine the earliest visible evidence of the disease, and thus learn more of its characteristics.

THE DEVELOPMENT OF A METHOD

Since 1933 all students entering the University of Wisconsin and reacting to 1 mg. or less of Old Tuberculin have received at the time of their enrollment a single 14 x 17 inch roentgenogram of their lungs. Thereafter, at intervals of from three to eighteen months, all infected students receive fluoroscopic examinations of their lungs.[4] As a result of this experience (1) a conviction developed that the roentgenoscopic method of examination had certain advantages over both the routine single and the stereoscopic films.

Proof of the advantages and the adequacy of lung roentgenoscopy necessitated the construction of an apparatus which would make it possible to take a roentgenogram with the roentgenoscopic unit to show what was seen on roentgenoscopy. A casette holder capable of being attached to the anterior part of the fluoroscopic screen was built, which, with the aid of a hand timer, permitted a roentgenogram of a localized area of a lung to be made. The roentgenogram served as a permanent record of what was seen on the fluoroscopic screen, and made possible comparisons with large single and stereoscopic films taken in the routine positions.

APPARATUS

The relatively crude apparatus originally built has been described (2). To facilitate easy and more adequate localization of the lesion for roentgenography, a mechanical device was designed and built which makes it possible to centre two screens, one for fluoroscopy and one for spot roentgenography, over a localized area of the body. The apparatus now being used is shown in figures 1 and 2. Both screens, it will be seen, are

[4] Students failing to react to tuberculin are retested at yearly intervals.

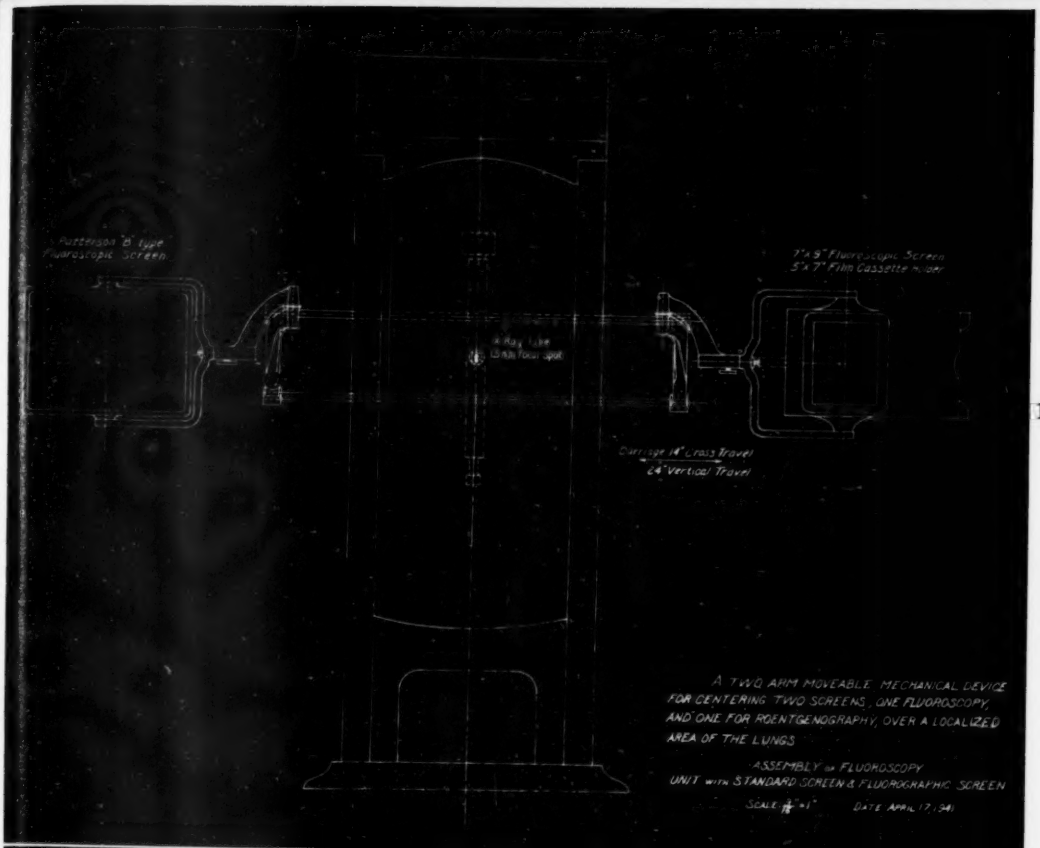

Patterson 'B' type
Fluoroscopic Screen
7"x 9" Fluoroscopic Screen
5"x 7" Film Cassette Holder
X Ray Tube
(Small Focal Spot
Carriage 14" Cross Travel
24" Vertical Travel
A TWO ARM MOVEABLE MECHANICAL DEVICE
FOR CENTERING TWO SCREENS, ONE FLUOROSCOPY,
AND ONE FOR ROENTGENOGRAPHY, OVER A LOCALIZED
AREA OF THE LUNGS
ASSEMBLY of FLUOROSCOPY
UNIT with STANDARD SCREEN & FLUOROGRAPHIC SCREEN
SCALE 1/8"=1" DATE APRIL 17, 1941

FIG. 1

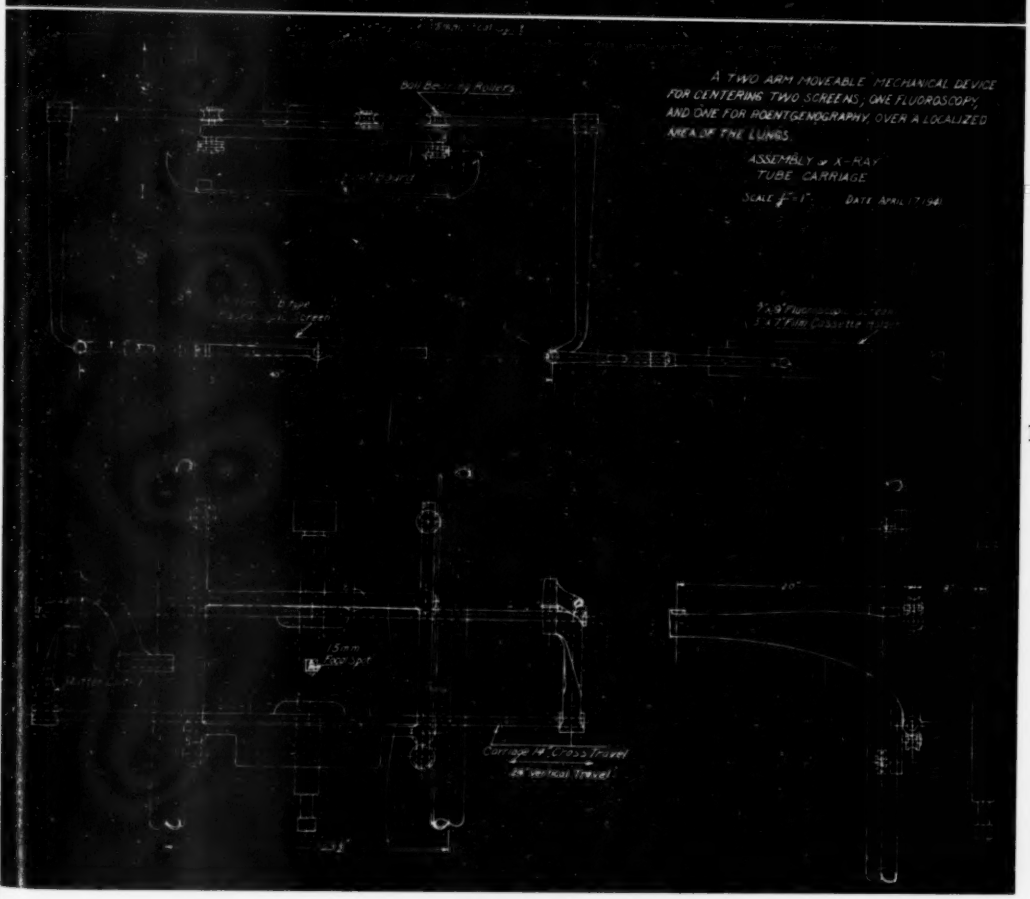

A TWO ARM MOVEABLE MECHANICAL DEVICE
FOR CENTERING TWO SCREENS, ONE FLUOROSCOPY,
AND ONE FOR ROENTGENOGRAPHY, OVER A LOCALIZED
AREA OF THE LUNGS
ASSEMBLY of X-RAY
TUBE CARRIAGE
SCALE 1/2"=1" DATE APRIL 17 1941
Carriage 14" Cross Travel
24" Vertical Travel

FIG. 2

FIGS. 1–2

attached to the tube by means of two side arms. After a lesion has been localized by means of the large fluoroscopic screen, this screen can be swung out of position and the small 7 x 9 inch screen swung into the same position. Since the centres of both screens describe arcs of equal circumference from points on the tube carriage equidistant from the focal spot of the tube (figure 2), the portion of the lung under scrutiny is in the same relative position regardless of which screen is swung into position. After a complete roentgenoscopic survey of the lungs had been made and an infiltrate found, the unit holding the small fluoroscopic screen and casette allows the lesion to be definitely located before the casette is shoved into position and the 5 x 7 inch film exposed. The time exposure, kilovoltage and milliamperage automatically change to the values previously set for them on the control unit when the casette is moved into position. The apparatus with its 1.5 mm. focal spot tube permits 15 milliamperes to be used. The time of exposure is usually one-tenth of a second, and the kilovoltage is varied from 64 to 90 according to the thickness of the chest. Without the advantage of a Patterson B type screen and a fine focal spot tube, small lesions in the lungs may escape detection.

The advantages of a freely movable fluoroscopic screen and casette holder should be emphasized. The joints holding the fluoroscopic screens should allow free movement laterally, proximally, distally and backward and forward. Furthermore, the joints should allow the screens to be tilted. Easy maneuverability of the fluoroscopic screens is a desirable attribute in roentgenoscopic study of the lungs. It is especially appreciated when certain small lesions are encountered which lie in areas of the lungs not readily brought into position to show them to their best advantage. The position of patient and screen is so important that not infrequently more than one spot roentgenogram must be taken before a film is obtained that shows the lesion to its best advantage. Once in position, the apparatus should be such that a roentgenogram may be quickly and adequately taken. The carriage holding the two screens and X-ray tube should be properly counterbalanced and should be equipped with sufficient roller bearings to permit free movement with a minimum of exertion, so that the examiner can direct his entire attention to the detailed examination of the lungs. Nothing is more disconcerting in the process of a roentgenoscopic examination, during which the patient is almost constantly being maneuvered into various positions, than to be hampered by a cumbersome and unresponsive apparatus.

FACTORS FAVORING ROENTGENOSCOPY

The adequacy of the roentgenoscopic examination of the lungs depends on several factors. Among these is the position of the patient in relationship to the tube and fluoroscopic screen. The number of positions from which different parts of the lungs may be viewed is limited only by the care and thoroughness with which the examiner does his job. The importance of the relationship of the tube (light source), object (lung lesion), and the screen can best be illustrated diagrammatically (see figure 3). A small lesion may not be dense enough when it is close to the source of light (focal spot) to cast on the fluoroscopic screen or X-ray film a shadow sufficiently intense to make its definition possible. When the same lesion is placed close to the screen or X-ray film, it may cast a shadow which is readily visible. Figure 4 illustrates such a case. The image on the stereoscopic films was not definite enough to allow interpretation. There was, however, no question of its presence on roentgenoscopic examination in the posteroanterior position. The two spot films on the left in figure 4 show an enlarged and faint image (object close to source of light, figure 3) hardly intense enough to allow interpretation. The two spot films on the right show a smaller and more definitely defined image (object close to screen, figure 3).

Another case (figure 5) illustrates more boldly the effect of the tube, object and screen relationship on the size and density of the image. The spot roentgenogram on the left shows the lesion greatly magnified with definition indistinct. The spot roentgenogram on the right shows the same lesion well defined and only slightly magnified.

Another factor, already mentioned, is the size of the focal spot. To what extent the size of the focal spot indicates the size and density of a lesion is illustrated in figure 6. With a large focal spot tube a small lesion is less magnified, and it may be so indistinct in outline, because of blurring resulting from the shadow-limiting rays, that interpretation is impossible (see figure 3). On two occasions lesions found with a 1.5 mm. focal spot tube, were not sharply enough defined to warrant interpretation with the 4 mm. focal spot tube. On a third occasion a lesion in the clavicular area seen in both the anteroposterior and posteroanterior oblique views with a 1.5 mm. focal spot, could be seen only in the anteroposterior position with a larger focal spot tube. Further comparisons and studies are necessary to determine to what extent the focal spot influences the definition of the lesion. Fortunately, roentgenoscopy and spot roentgenography, because

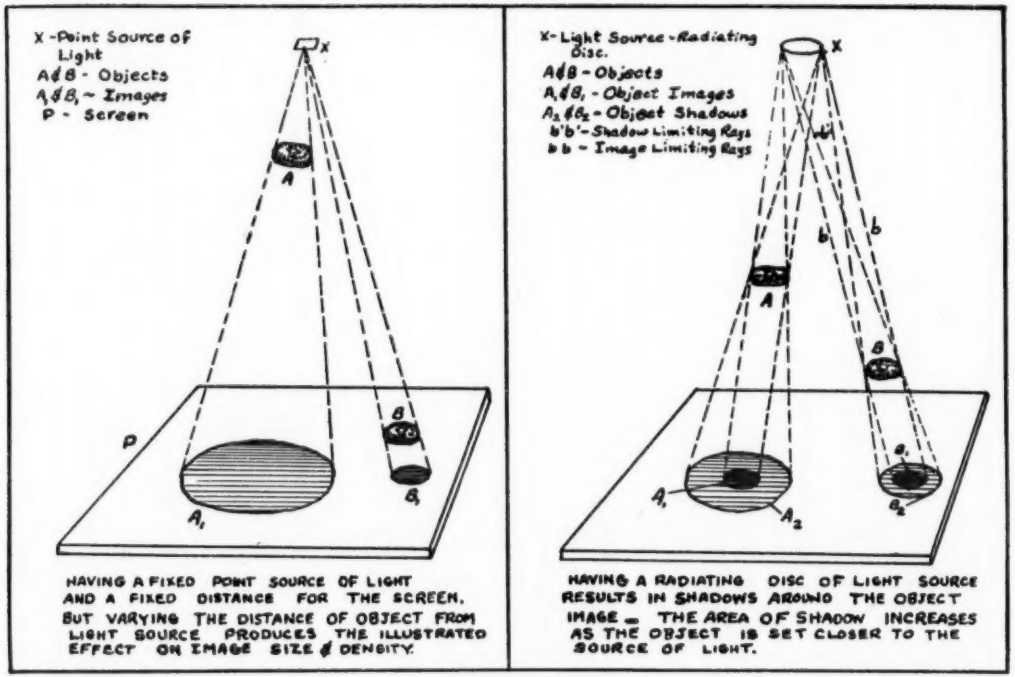

X - Point Source of Light
A & B - Objects
A1 & B1 - Images
P - Screen
X
A
B
P
A1
B1
HAVING A FIXED POINT SOURCE OF LIGHT AND A FIXED DISTANCE FOR THE SCREEN. BUT VARYING THE DISTANCE OF OBJECT FROM LIGHT SOURCE PRODUCES THE ILLUSTRATED EFFECT ON IMAGE SIZE & DENSITY.
X - Light Source - Radiating Disc.
A & B - Objects
A1 & B1 - Object Images
A2 & B2 - Object Shadows
b'b' - Shadow Limiting Rays
b b - Image Limiting Rays
X
b'
b
b
A
B
A1
A2
B2
HAVING A RADIATING DISC OF LIGHT SOURCE RESULTS IN SHADOWS AROUND THE OBJECT IMAGE — THE AREA OF SHADOW INCREASES AS THE OBJECT IS SET CLOSER TO THE SOURCE OF LIGHT.

FIG. 3

the patient is placed close to the source of energy, do not require milliamperes in excess of fifteen, which permits the use of a small focal spot tube. Furthermore, because the patient is always relatively close to the

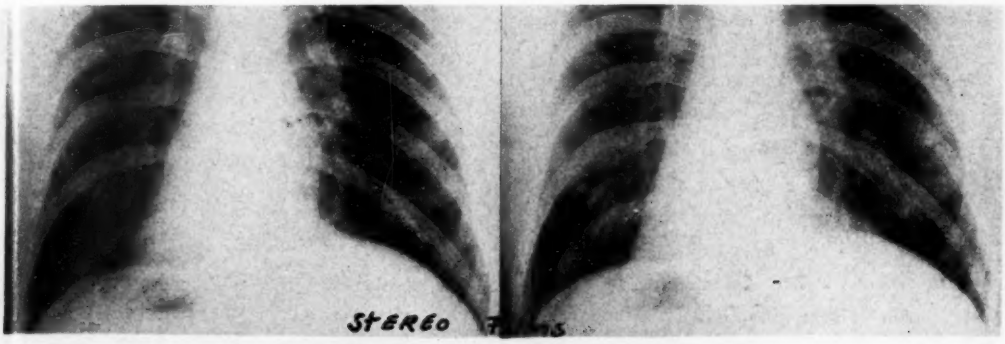
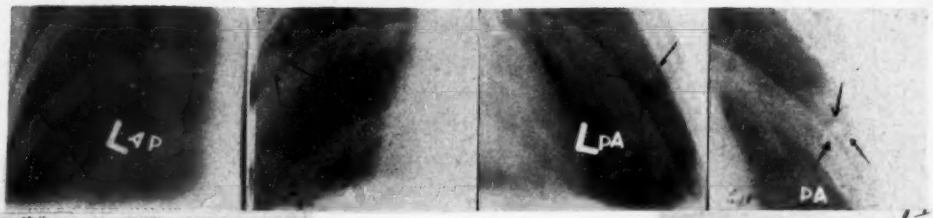


FIG. 4



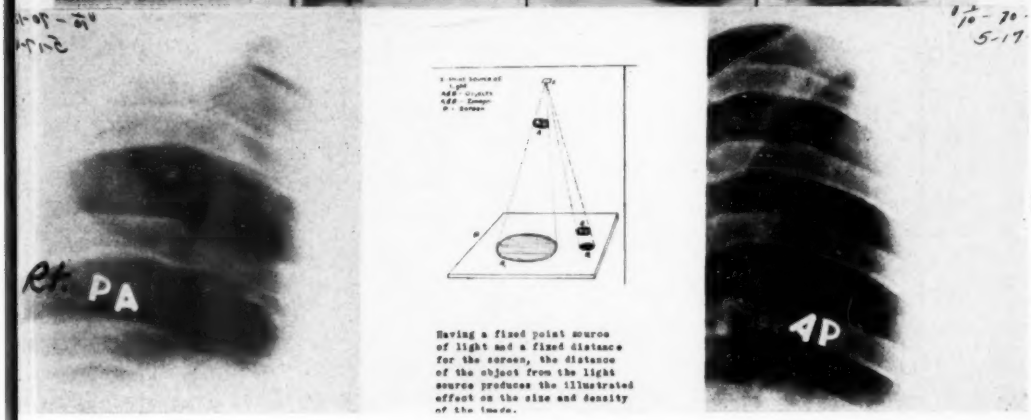

Rt. PA
Having a fixed point source of light and a fixed distance for the screen, the distance of the object from the light source produces the illustrated effect on the size and density of the image.
AP

FIG. 5

FIGS. 4–5

small focal spot, the lesion, unless very small, is usually magnified, even distorted. The magnification has its advantage in finding and recording minimal and subminimal lesions not large enough to allow interpretation on the routine films (figures 4, 8 and 12).

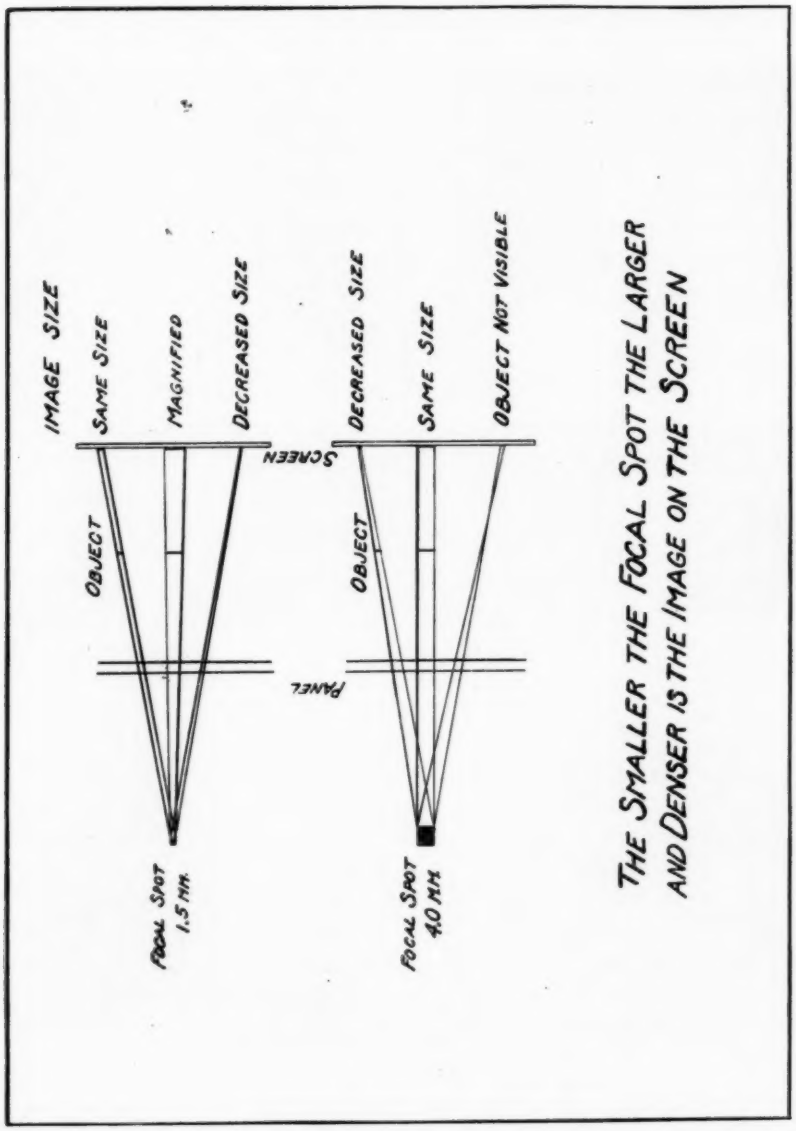


IMAGE SIZE
SAME SIZE
MAGNIFIED
DECREASED SIZE
SCREEN
DECREASED SIZE
SAME SIZE
OBJECT NOT VISIBLE
OBJECT
OBJECT
PANEL
FOCAL SPOT 1.5 MM
FOCAL SPOT 4.0 MM
THE SMALLER THE FOCAL SPOT THE LARGER AND DENSER IS THE IMAGE ON THE SCREEN

FIG. 6

Another advantage of roentgenoscopy deserving consideration is that the milliamperage and kilovoltage may be varied to make a lesion more clearly visible. This may be of especial value in studying the lungs of children. Recently a five-year-old child was found to have increased hilum shadows, presumably due, because of recent close contact with a tuberculous mother, to tuberculosis of the hilar lymph nodes. No parenchymal shadow could be seen on the routine films. However, roentgenoscopy clearly revealed an infiltration in the clavicular area. Spot roentgenograms taken on the first occasion failed, as did the routine films, to show the lesion. By decreasing the kilovoltage the lesion as seen by roentgenoscopy was made visible on the roentgenogram.

CASE PRESENTATIONS

The advantages of the proper position and the importance of viewing the lungs in several positions, thus bringing into view lesions at the periphery of the lung and those hidden by the bones or other structures, the advantage of magnification of small lesion and the limitations of even the 14 x 17 inch stereoscopic films are revealed by the following cases.

Figure 7 shows a 14 x 17 inch stereoscopic roentgenogram of the chest and two 5 x 7 inch spot films of the right apex. The spot films were taken in the posteroanterior and the anteroposterior oblique positions. The roentgenologist's interpretation of the stereoscopic films is as follows: "As compared with the single film of October, 1940, the present study shows continuance of a moderate peribronchial accentuation of diffuse type. There is in addition evidence of a small opacity in the extreme summit of the right apex which seems to contain a small amount of granular calcification. There is also a pleural density in the extreme summit of the left apex. Both of these shadows may have been present in the flat film but obscured by overlying ribs. They evidently represent localized pleural reaction with a very minute amount of subpleural involvement which is becoming calcified on the right." The spot film shown on the left, taken in the posteroanterior view, shows a magnified lesion at the extreme right apex, the outlines of which are indistinct and blurred. The spot film taken in the anteroposterior view shows a less magnified lesion with sharply defined outlines, probably representing small apical cavities. In the light of the tube, object and screen relationships, represented in figure 3, it is apparent that the lesion is in the posterior part of the apex of the right lung; this is indicated by greater magnification and less definition in the posteroanterior view and by less magnification and better definition in the anteroposterior view. In the large 14 x 17 inch films the apices were largely obscured by the overlying first and second ribs and accurate interpretation was therefore impossible.

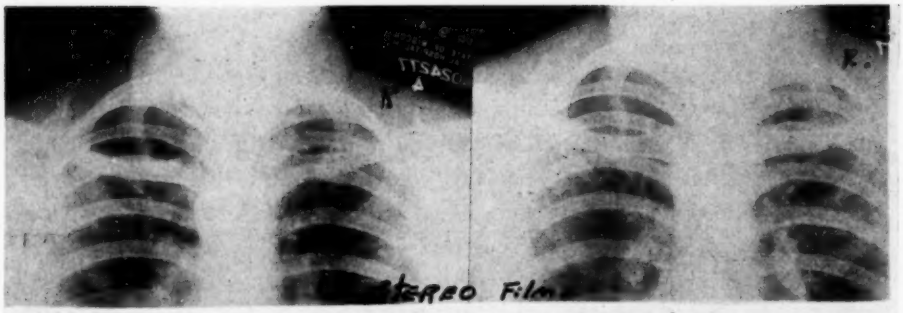
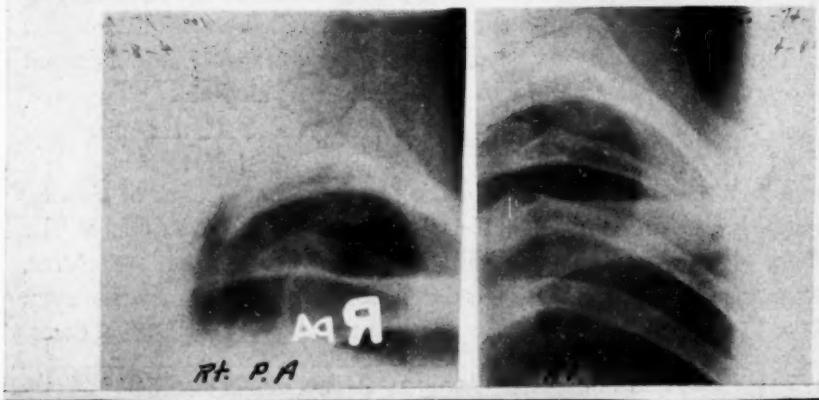


FIG. 7



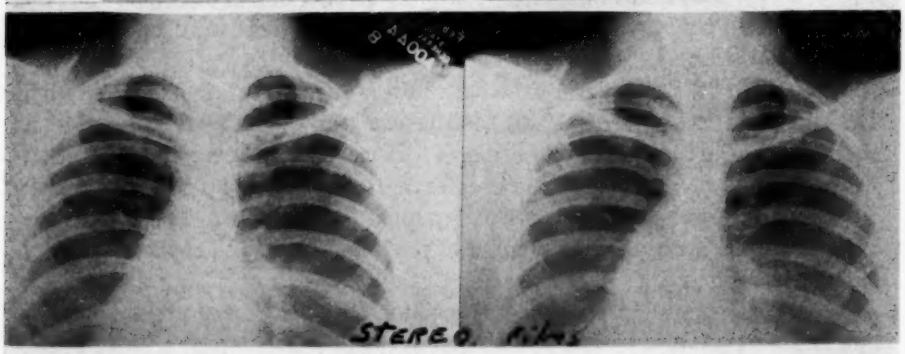
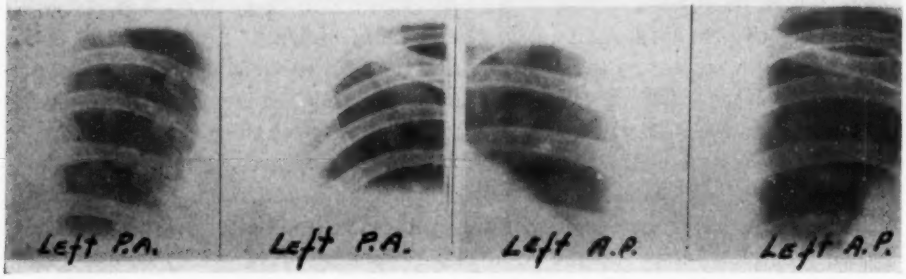


FIG. 8



FIGS. 7 AND 8

Figure 8 reproduces the films of a student nurse whose tuberculin test was negative until June, 1940. Routine films and roentgenoscopy in June and December of 1940 were negative. After she had completed her nurse's training course in February, 1941, stereoscopic films of her lungs were taken which were interpreted by an able roentgenologist as follows: "The present study shows well aerated lung parenchyma. The heart is within limits of normal in size. There is little fullness of its pulmonic arch. The hilum shadows

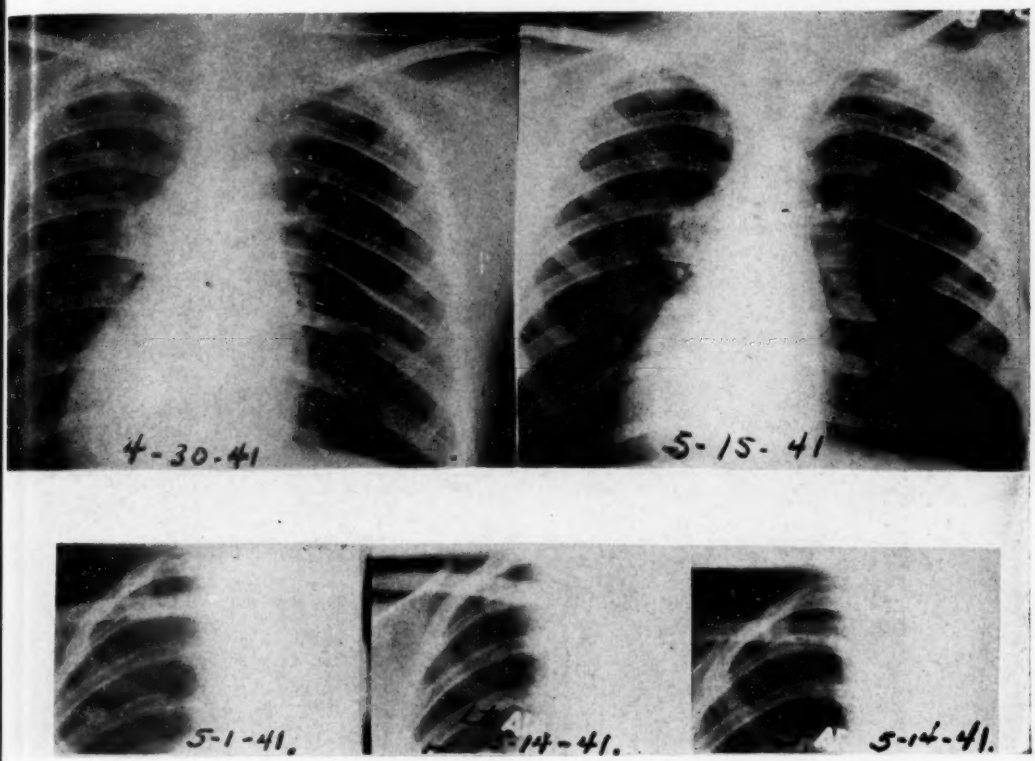


FIG. 9

appear normal. There is a question of small calcified Ghon tubercle in the right base. Domes of the diaphragm are at normal levels and the sulci are clear. Conclusion: The chest is negative for significant parenchymal disease. Questionable abnormal cardiac silhouette."

The four spot films show a lesion as it appeared on roentgenoscopic examination. The two taken in the anteroposterior view show a shadow that is smaller and more dense than the two taken in the posteroanterior view, indicating that the lesion is in the posterior part of the lung. In this case a small

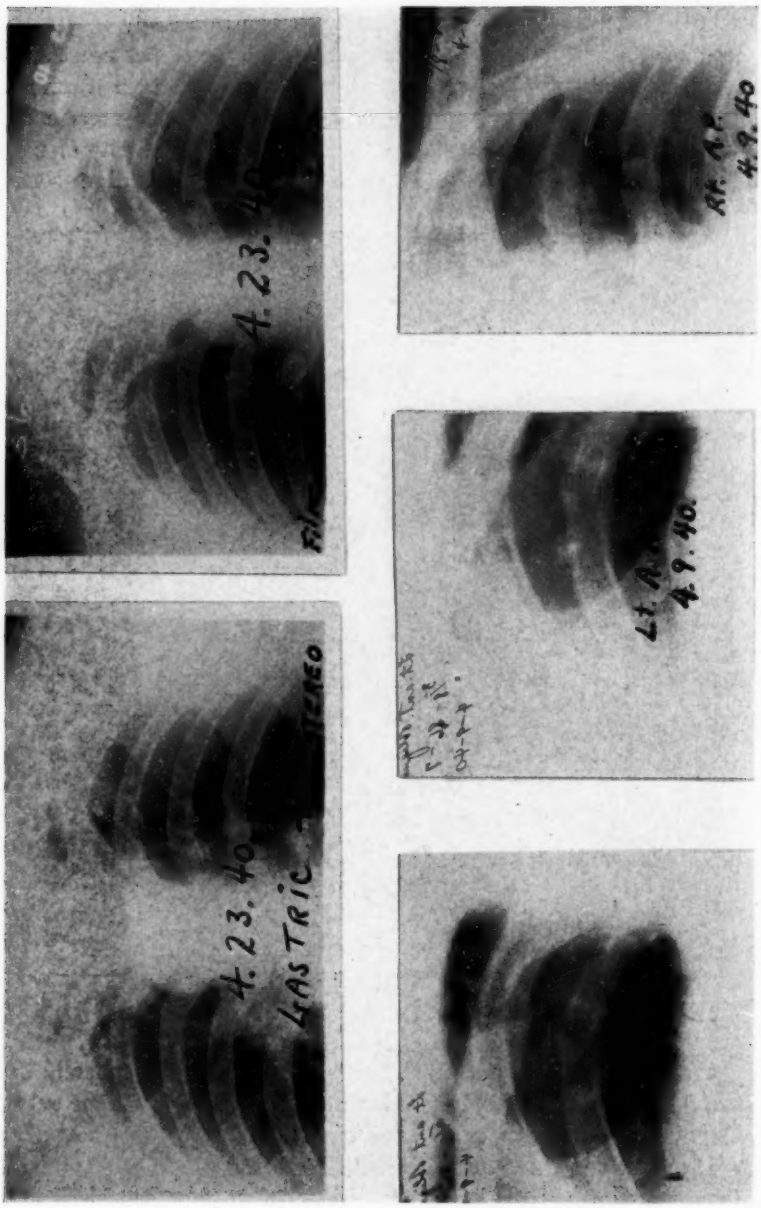


FIG. 10

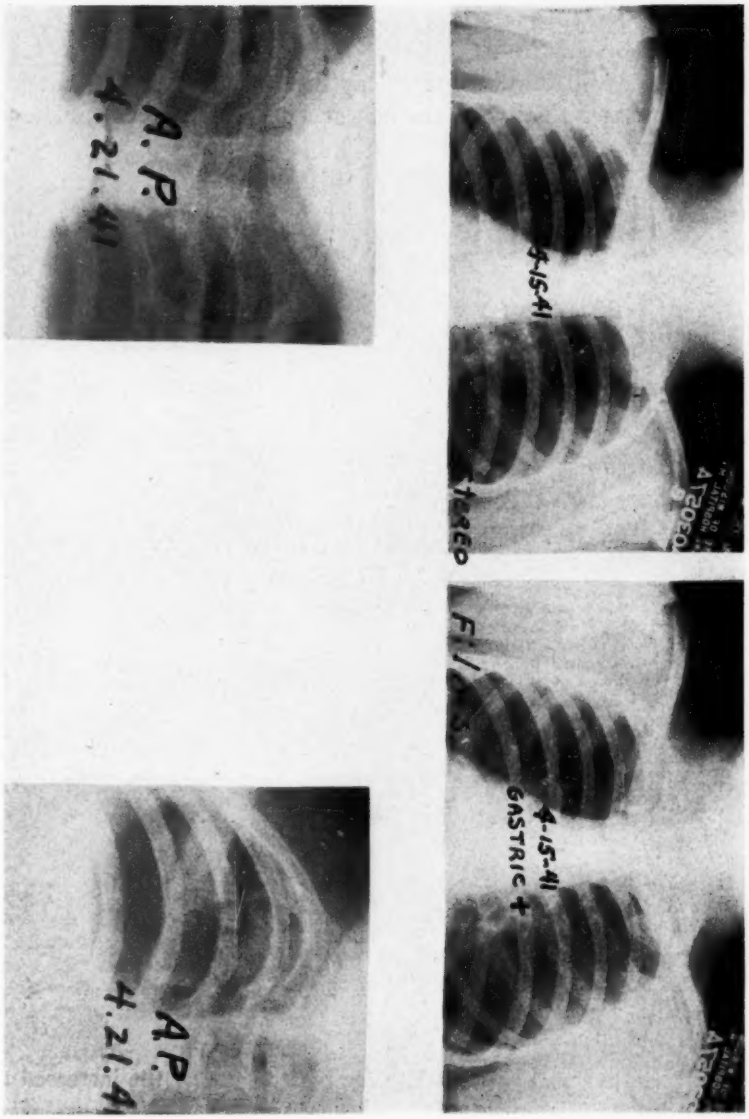


FIG. 11

active tuberculous lesion, as indicated by guinea pig inoculation with the fasting gastric contents, was obscured by a rib to an extent sufficient to escape detection with 14 x 17 inch stereoscopic films.

The plane in which a lesion lies may determine whether or not it is dense enough to cast a shadow on the film or fluoroscopic screen. Figure 9 shows

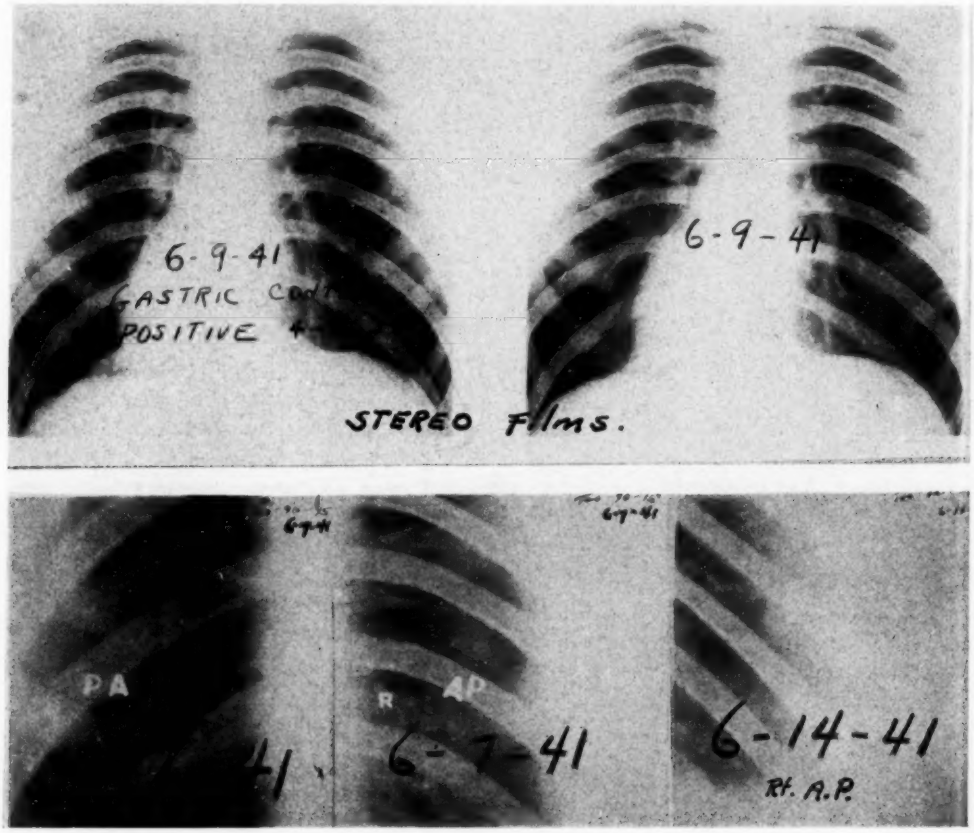


FIG. 12

two large films in which there is some mottling along the increased trunks in the left first anterior interspace. To what extent a rather dense infiltrate was brought into view when the lesion was placed in another plane is shown by the spot roentgenograms.

The extent to which lesions in the apex and clavicular regions are not visible in large 14 x 17 inch stereoscopic films, because of overlying ribs, is illustrated

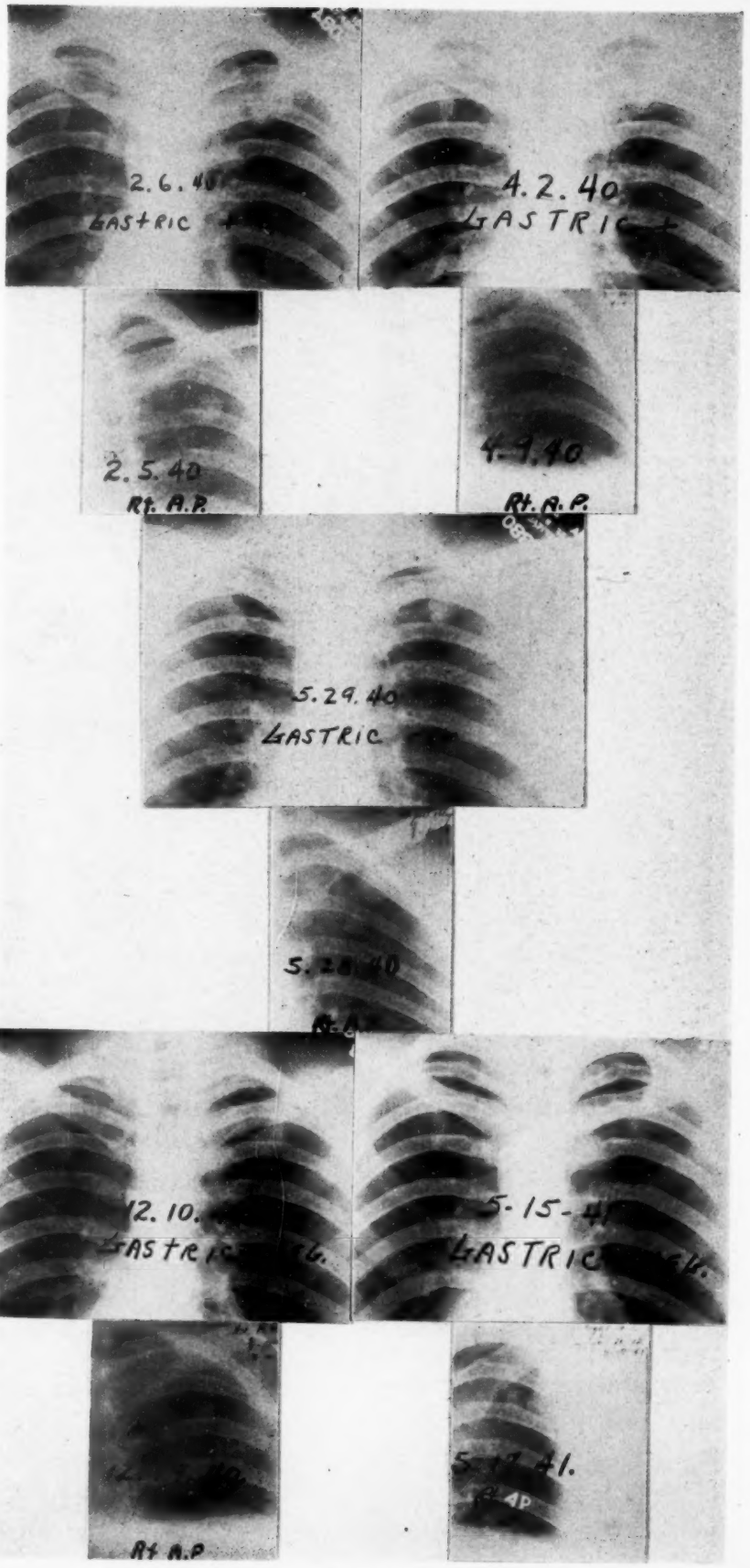

2.6.40
GASTRIC
4.2.40
GASTRIC
2.5.40
Rt. A.P.
4.9.40
Rt. A.P.
5.29.40
GASTRIC
5.15.41
GASTRIC
Rt A.P

FIG. 13

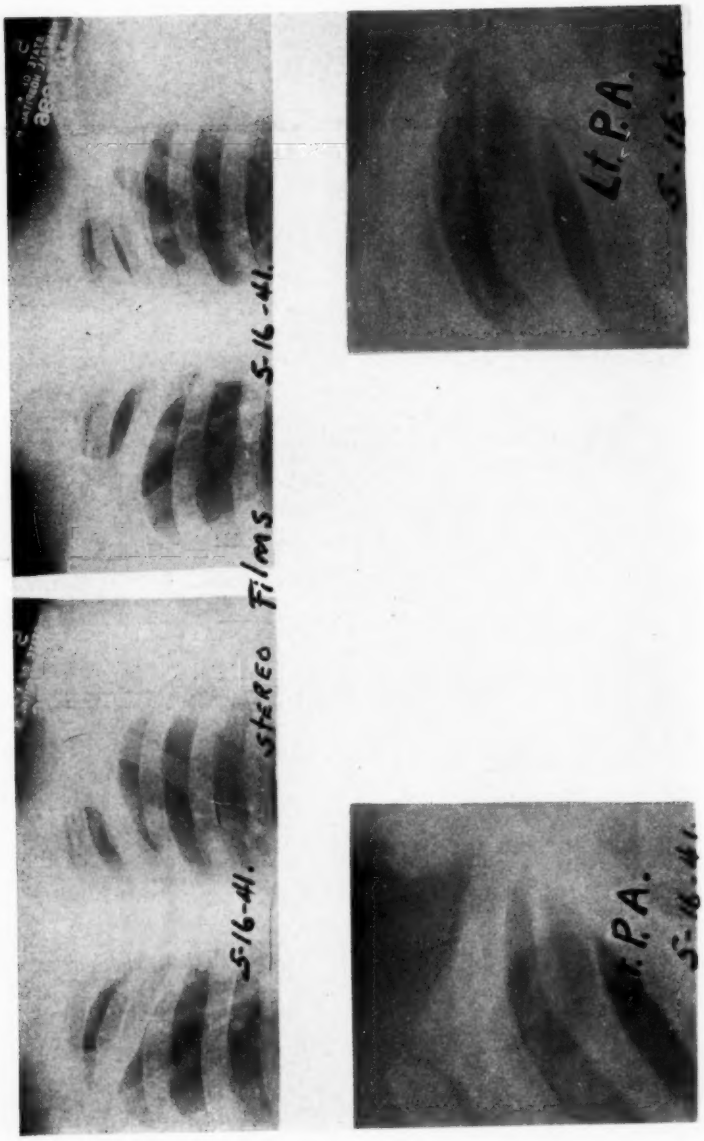


FIG. 14

in figures 10 and 11. Figure 10 shows the stereoscopic and spot films of a medical student who had recently been discharged from a sanatorium when serial roentgenograms revealed little change of the small visible infiltrate. The spot films, however, showed a rather extensive bilateral clavicular infiltration and the gastric contents were found positive by guinea pig inoculation for tubercle bacilli.

The stereoscopic films in figure 11 were interpreted as follows on May 13, 1941: "The cardiac size and contour are normal. The domes of the diaphragms are smooth and the sulci are clear. There appears to be a small amount of calcification in the lymph nodes in both hila. There appears to be thickened pleural caps and a small amount of infiltration in both apices. The bronchial markings are somewhat accentuated. Conclusion: Minimal apical pulmonary tuberculosis." The prints, figure 11, indicate that the apices are largely obscured by the bony framework of the thorax. The spot films below show what was easily seen on the fluoroscopic screen—an extensive soft infiltrate at both apices with definite cavitation in the right apex. The gastric contents were positive by guinea pig inoculation.

Figure 12 represents the case of the boy already referred to who developed a spontaneous pneumothorax in April, 1941, whose tuberculin reaction had become positive, and whose gastric contents were positive by guinea pig inoculation before the lesion became visible. Though the stereoscopic films of June 9, 1941 fail to show the lesion, it was clearly defined by roentgenoscopy as shown by the spot roentgenograms.

Figure 13 shows the adequacy of spot film roentgenography in studying the progress of a lesion. Especially where the lesion is in the clavicular area, as it was in this case, the method has an advantage over the large films taken in the routine position, where the lesion is repeatedly obscured by the bones.

To what extent a small pneumothorax at the extreme apex may be obscured by overlying ribs is shown in figure 14. The roentgenologist's interpretation of May 17, 1941 follows: "The pneumothorax has disappeared on both sides and both lungs are fully expanded. There is visible now some irregular scarring over the apical summits evidently in the visceral layers of pleura. Elsewhere the lung fields are quite clear and normal." Note how distinctly the persisting pneumothorax was determined by roentgenoscopy and spot roentgenography.

DISCUSSION

To-day great reliance is placed on the single or stereoscopic roentgenogram taken in the routine posteroanterior position. The limitations of the routine chest roentgenogram cannot be fully appreciated until

comparison is made with roentgenoscopy. Reliance on posteroanterior roentgenograms has reached a point that miniature photographs of the fluoroscopic screen are being substituted for 14 x 17 inch roentgenograms. Such a tendency should be viewed with more caution and less enthusiasm. Use of the miniature photographs is perhaps justifiable on the basis of economy, but if the method is used its limitations must be more widely appreciated, especially if the small infiltrate is to be found. Enlargement by magnification of the image which is possible by roentgenoscopy and spot roentgenography rather than reduction of the image appears more tenable.

Unfortunate is the fact that a tendency has developed to delete the tuberculin test where mass surveys are being made with miniature photographs of the fluoroscopic image. It must be remembered that the tuberculin test is the earliest indication that tubercle formation has occurred somewhere in the body. Since this is true it is important that tuberculin tests be repeated at yearly or more frequent intervals on all individuals who are negative. When this routine is followed the approximate time of occurrence of infection is known. The physician knowing when infection occurs has the opportunity by repeated roentgen ray study to learn more of the pathogenesis of the disease.

There is little justification for the interpretation of a shadow on a miniature photograph as suspicious for tuberculosis without the knowledge that tuberculous infection has occurred. Such practice alarms the patient and does not lead to accuracy of diagnosis. The fact is appreciated that the infected individual may lose his allergic response to tuberculin, but in no instance among 30,000 students studied has one been found with tubercle bacilli in his secretions from the respiratory tract, as proven by guinea pig inoculation, who failed to react to 1 mg. of Old Tuberculin given intracutaneously. Cases have occurred in which acid-fast bacilli have been found, but these were not pathogenic to guinea pigs and, therefore, were probably not tubercle bacilli.

As already stated, because the tuberculin test is the earliest and most delicate test to indicate that tubercle formation has occurred somewhere in the body, it should not be omitted even when mass surveys are conducted with miniature photographs. Low cost of miniature films makes the tuberculin test no less valuable. Efforts and money now expended in studying all individuals roentgenologically without knowing which are infected could more adequately be directed in doing tuberculin tests and

more forcefully directing our efforts by repeated roentgen ray examination of the infected. It may be more practical, but it is not good medical practice to make mass roentgen ray surveys without knowledge of which patients are infected.

The frequent practice in mass surveys of attempting to designate by roentgenographic examination which lesions typify significant pulmonary tuberculosis and which typify arrested disease is hazardous, unfortunate and leads to error of diagnosis. The fact should be emphasized that minuteness of a tuberculous lesion is not an indication of benignity. So-called further study of a case which includes history, physical examination, more roentgenograms and laboratory procedures should not be considered complete unless the fasting gastric contents are aspirated on three successive mornings and guinea pigs are inoculated. This critical method of examination is the most accurate test (3, 4) now available to determine the status of a lesion, notwithstanding the fact that it may not always give the correct answer. The presence of tubercle bacilli as determined by guinea pig inoculation indicates at once that with few exceptions the lesion seen on the roentgenogram is both tuberculous and pathologically active.

CONCLUSIONS

The opinion is expressed that the roentgenoscopic examination of the lungs in individuals of normal proportions is the most efficient method of finding small infiltrates in the lungs. Small lesions lying in the apices, clavicular areas and in the lung periphery are more frequently missed, even when the 14 x 17 inch stereoscopic films are used, than is generally appreciated. Small infiltrates in other parts of the lung are occasionally obscured by the ribs or are of insufficient density to be found by the routine film. That these small lesions are significant is indicated by the frequency with which the gastric contents are found positive by guinea pig inoculation.

The importance of using a freely movable, easily responding apparatus equipped with a fine focal spot tube and Patterson B type screen is emphasized. Factors favoring roentgenoscopy and spot roentgenography are discussed.

Cases are presented which show the adequacy of the method, and its advantage over 14 x 17 inch films, both single or stereoscopic, taken in the routine posteroanterior position.

The equipment is not expensive, the small films are economical and operation of the apparatus is relatively simple.

It is predicted that roentgenoscopy of the chest will some day be regarded as the most accurate method in finding small infiltrates in the lungs. Its use will be limited primarily to those who use it repeatedly and become proficient by experience. The method will appeal especially to the roentgenologist and the medical specialist who wishes to study in detail the lungs of patients.

CONCLUSIONES

Exprésase en este trabajo la opinión de que el examen roentgenoscópico de los pulmones en los individuos de proporciones normales representa el método más eficaz para descubrir la existencia de pequeñas infiltraciones en los pulmones. Las pequeñas lesiones radicadas en los vértices, zonas claviculares y periferia pulmonar son pasadas por alto más frecuentemente que lo que se suele imaginar, aun utilizando las películas roentgenoscópicas de 35 por 42.5 cm. En otras partes del pulmón, los pequeños infiltrados se ven a veces oscurecidos por las costillas, o no muestran un espesor suficiente para que los descubra la película corriente. La importancia de estas lesiones pequeñas queda indicada por la frecuencia con que el contenido gástrico resulta positivo al inocularlo en el cobayo.

Recálcase aquí la importancia de emplear un aparato muy movible y de fácil manejo, provisto de un tubo de enfocación delicada y de una pantalla tipo Patterson B. Discútense los factores que favorecen la roentgenoscopia y la roentgenografía en placas.

Se presentan casos que revelan lo adecuado que resulte este método, y su superioridad sobre las películas tanto aisladas como estereoscópicas, obtenidas en la corriente posición postero-anterior.

La instalación no es costosa, las películas pequeñas resultan económicas, y el funcionamiento del aparato es relativamente sencillo.

Predícese que la roentgenoscopia torácica será considerada algún día como el método más exacto para descubrir las pequeñas infiltraciones de los pulmones, pero limitándose su empleo primordialmente a los que lo utilizan repetidamente y son avezados en el manejo. El método interesará especialmente al roentgenólogo y al especialista médico que desea estudiar a fondo los pulmones de los enfermos.

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TUBERCULOSIS CONTROL PROGRAM IN MEXICO[1]

DONATO G. ALARCÓN[2]

Five years ago, by invitation of the National Tuberculosis Association, I had the honor of attending the 1936 annual meeting of this Society to read a paper on the campaign against tuberculosis in Mexico.

Again I have the privilege of presenting before you an address on the program against tuberculosis in my country and it was by suggestion of the Directors of this Association that the subject has been chosen. This suggestion is a proof of the great interest aroused among the members of your select group for our activities in tuberculosis control beyond the Rio Grande, that have been developed since I first appeared before this audience.

I have to explain that, since I started the work of the tuberculosis sanatorium as medical director, I became disconnected from the Department of Public Health and all our work was done under the administration of the Public Welfare as it is done to-day. But very recently I was invited by the head of the Public Health Department, Dr. Victor Fernandez Manero, to coöperate in a Federal Tuberculosis Campaign.

As I informed this audience five years ago, our program in Mexico has some peculiarities which make it different from your ways for doing the same work in the United States. I shall not repeat *in extenso* these characteristics but I shall try to summarize them:

To-day in Mexico the campaign is almost entirely in charge of the governmental agencies represented by the Department of Public Health and the Ministry of Public Welfare. This is an important difference as compared to the United States program which is almost completely developed under the auspices of private institutions and associations like the National Tuberculosis Association. It is through the Department of Public Health that the campaign is made according to the plan already described years ago and the means used as everywhere are the direct and the indirect ones. The direct means are the search of pa-

[1] Presented before the Medical Section at the 37th annual meeting of the National Tuberculosis Association, San Antonio, Texas, May 5, 1941.

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tients by the dispensaries to lead them to institutions which may take care of the definite case, such as sanatorium, hospital, preventorium, etc. Besides, the dispensaries take care of the ambulatory treatment of the benign, well tolerated type of disease, in cases which can obtain real benefit from this kind of treatment. As our hospitals and sanatoria are far from being sufficient to admit the great number of active patients, this form of work is one of the most important in our country.

Our experience in ambulatory treatment is most extensive due to this circumstance. We treat a considerable number of cases taking relative rest at home and attending the dispensary for medical care in greater number than is common in other countries. This special condition of our work has given us some different concept of the value of this ambulatory care of the tuberculous, although we admit that institutional care is by far more desirable than the dispensary treatment.

The limited number of beds available for active cases is used according to the urgency of admission. We have to limit the stay within our sanatoria as much as possible in order to make each bed available for more patients. Also our work within our sanatorium has some special features. It is of the hospital-sanatorium type. The work is preferably oriented toward collapse procedures, and within this kind of treatment our procedures are most active.

A review of the work done for instance at the tuberculosis sanatorium in Mexico City reveals that, with a really small capacity, our surgical work for every hundred beds is exceedingly greater than that of the majority of the sanatoria and hospitals in New York. That depends not so much on the attitude of our specialists, nor on any belittling concept of the prolonged rest as a main form of treatment, but on the stage in which the majority of cases come to the sanatorium.

Sixty-eight per cent of our cases are bilateral on admission. Fifty per cent have cavities visible on the roentgen film.

Nearly 12 per cent have bilateral cavities. Only 5 per cent have moderate sized infiltrates in the pneumonic stage. This is on account of the lack of education and on account of the lack of facilities to make early diagnosis. In this circumstance we have no choice and our institution has made itself a centre of the most exhaustive work. With only 220 beds to-day our work surpasses that of such institutions as Metropolitan and Belleview Hospitals of New York in surgical procedures of tuberculosis.

These simple numbers give you an idea of the necessary attitude of

the specialist in Mexico. We have to work fast and steadily if we are to expect fairly good results on this group of the advanced tuberculous. And we are very satisfied with the results so far obtained.

Another activity of the dispensary is the selection of patients for admission to the several institutions according to their type, age, etc.

As indirect means we have the educational work of the dispensaries concerning the disease which is carried out by the Bureau of Health Education of the Department of Health. A bureau for the improvement of housing and the Committee on Housing Conditions recently founded are starting a drive to improve these conditions in Mexico.

The National Food Commission is also studying the more practical means for modifying the unfortunate situation of our population in this regard.

To-day our armamentarium against tuberculosis has not gained much as compared with that of five years ago. The number of dispensaries in the Republic has increased. Now we count 8 in Mexico City and 25 more in the states. On the other hand we have less than 1,000 beds in Mexico and a few private sanatoria with about 100 beds.

Dr. Fernandez Manero, Head of the Department of Public Health, who has been appointed to his office this year, has undertaken the campaign with remarkable enthusiasm and I am able to testify that these activities have at last found a tireless promoter. In a few months gigantic strides have been made. Particularly a tremendous gain is noticeable in attracting private coöperation for the campaign.

Years ago I announced that our program included the creation of the National Committee against Tuberculosis. Now this Committee is working, consisting of a group of most outstanding men in financial, professional and social activities. This Committee has several bureaus: one for the financial side of the work, one for technical advice, one for educational purpose and another for social work. It has an executive group of directors and all its activities are sponsored and backed by the government through the Department of Public Health. As head of the Official Campaign I have been appointed the General Director of the Committee, but the institution has an autonomous function and is able to make any financial arrangements under its full responsibility by law.

With a realistic conception of the urgent needs the Committee decided to launch a drive to collect funds in order to build several hospitals, sanatoria, preventoria and rehabilitation centres. The program for this

year is to build a 300 bed hospital for tuberculous children, a 300 bed hospital for advanced tuberculosis, a preventorium for 300 children, a new pavilion at the Public Welfare Sanatorium with 100 beds, a colony for rehabilitation of former patients with a capacity for 200, all this in Mexico City, and outside of Mexico City two regional sanatoria will be built for the two main regions afflicted by tuberculosis: the Pacific and the Gulf coast. This program will add 1,700 beds to our armamentarium when completed and shall cost about five million pesos.

Two months ago the drive to obtain funds for this purpose was started and I have the pleasure of announcing that to-day we have at the disposal of the Committee over three million pesos. The Committee is working enthusiastically and all of us in Mexico hope to complete this first phase of the program within a year. The National Committee is planning the use of BCG vaccine as a means to protect our children from tuberculous mothers. The laboratory shall be organized this year and the use shall start next year.

When this first phase is over we have to start another one: the creation of new institutions until the available beds are equal to the need of the population. If everything goes as is expected our total program to build hospitals will take only six years to be completed.

We realize that to solve the problem of tuberculosis it is necessary to face the multiple aspects of the campaign and to spend enormous amounts of money. It is impossible for a poor country, such as Mexico, to obtain such amounts from private coöperation only and therefore the Committee is studying the possibility of creating a special insurance against tuberculosis as compulsory means of raising funds in proportion to the magnitude of the problem.

In our population with tremendous differences in education, earnings and habits, it is impossible to provide for the needs of the communities if there are no means to distribute expenditures in the most fair, proportional and humane way. We believe that only through an adequate insurance plan we may find a clear way to reach our aims.

A seal sale campaign is also under careful study; it will be made this year, or early in the next, for the first time.

There are some peculiarities in our campaign which are worth while stressing: Our campaign is developed under very limited possibilities as far as acquisition of funds is concerned. The activities are mostly in charge of governmental agencies and only recently has private initiative contributed its effort and money.

To-day we have to face the therapeutic problem of the tuberculous, using the most effective procedures in order to shorten as far as possible the stay of patients within our hospitals. One of our beds is more valuable to us than it is for other communities, as these beds are very scarce. The campaign, started in Mexico two months ago, will allow us to meet satisfactorily the urgent need of beds in a few years if we keep up with the present pace.

This is our situation to-day and these our hopes for the future. Your work is our inspiration for we are aware of the tremendous improvement in the United States in the fight against tuberculosis and we believe that, following your steps, we are going to be as successful as you have been, but certain things must be done differently because our economic circumstances, education, attitude and habits are different.

TUBERCULOSIS CONTROL AMONG THE NORTH AMERICAN INDIANS[1,2,3]

J. G. TOWNSEND, JOSEPH D. ARONSON, ROBERT SAYLOR AND IRMA PARR

In order to combat a problem through a program of control, the extent of that problem must first be known. The early records of tuberculosis morbidity and mortality among Indians were unreliable and misleading, due to indifferent reporting, selected material, lack of general surveys and mortality data collected by teachers, traders, missionaries and other lay groups. In analyzing the causes of death among residents of Alaska, from the parish records of the Russian Orthodox Church, one is impressed by the frequency with which tuberculosis occurs as a cause of death and the infrequency with which pneumonia is given as a cause of death among Indians. On the other hand, among the white population pneumonia is frequently stated to have been the cause of death and tuberculosis as the cause of death is uncommon. After careful consideration, one is led to conclude that there has been exaggeration of the frequency with which tuberculosis occurred among Indians.

About six years ago the Indian Office, in coöperation with the Henry Phipps Institute of the University of Pennsylvania, initiated a program for the control of tuberculosis among Indians. Dr. Esmond R. Long was appointed consultant, as were other members of the Institute staff, and Dr. J. D. Aronson of the Institute was placed on full-time duty with the Indian Office to conduct a carefully controlled study of the value of Calmette-Guérin vaccine. Doctors and nurses of the Service were and are now detailed to the Institute for periods of study and training, and in-service conferences were developed whereby personnel from the Henry Phipps Institute led refresher courses in epidemiology, diagnosis and treatment for large groups of field personnel at various reservations. Thus was started a system of case-finding on a standardized basis.

[1] Presented before the Medical Section at the 37th annual meeting of the National Tuberculosis Association, San Antonio, Texas, May 5, 1941.

[2] From the Office of Indian Affairs, Department of the Interior, Washington, D. C., and the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[3] This investigation was aided by the National Institute of Health of the United States Public Health Service as part of a coöperative study.

It appeared highly desirable to have definite information indicating the extent of tuberculous infection and disease in areas where the value of BCG vaccine was to be determined. The incidence of tuberculous infection was determined by means of the intracutaneous tuberculin test. This test was carried out in the usual manner, with a sample of Purified Protein Derivative tuberculin kindly prepared for us by Dr. Florence Seibert. Fresh dilutions containing 0.000,02 and 0.005 mg. per 0.1 cc. were prepared daily from a 1 per cent tuberculin solution.

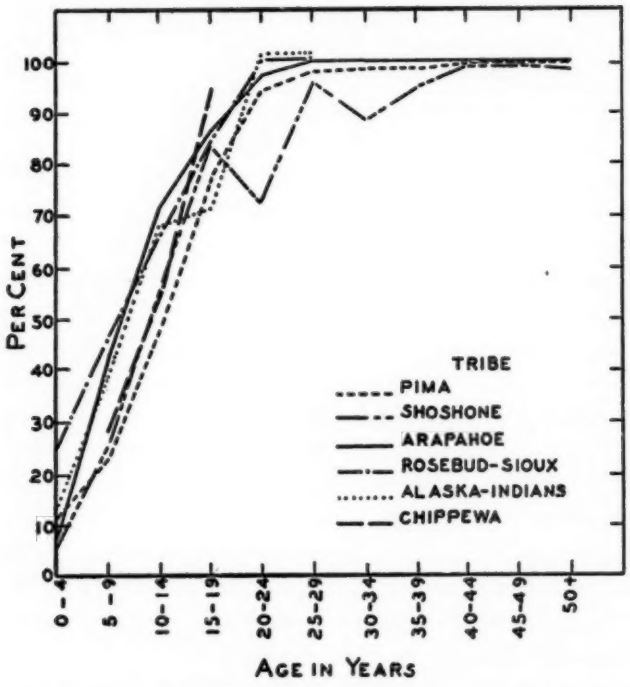

CHART 1. Tuberculin reaction among some Indian tribes.

The reactions were read after forty-eight hours and recorded in the usual manner. The results of these tuberculin tests carried out on a total of 8,420 persons among the Pima Indians of Arizona, the Shoshone and Arapaho Indians of Wyoming, the Sioux of South Dakota, the Thlingit, Haida and Tsimpsian Indians in southeastern Alaska and the Chippewa Indians of North Dakota, are presented graphically in chart 1.

It will be observed from this chart that the incidence of tuberculous infection for each five-year period is approximately the same for the

different tribes, and reaches approximately 100 per cent for the age of twenty-five years and higher. The incidence is not materially affected by climate, diet, social and economic conditions, tribal stock or degree of blood admixture.

The results of tuberculin tests among the Indians are compared in chart 2 with similar tests conducted by Aronson among 12,000 colored persons in some rural areas of the South and among 8,000 of the rural white population in some areas in Michigan.

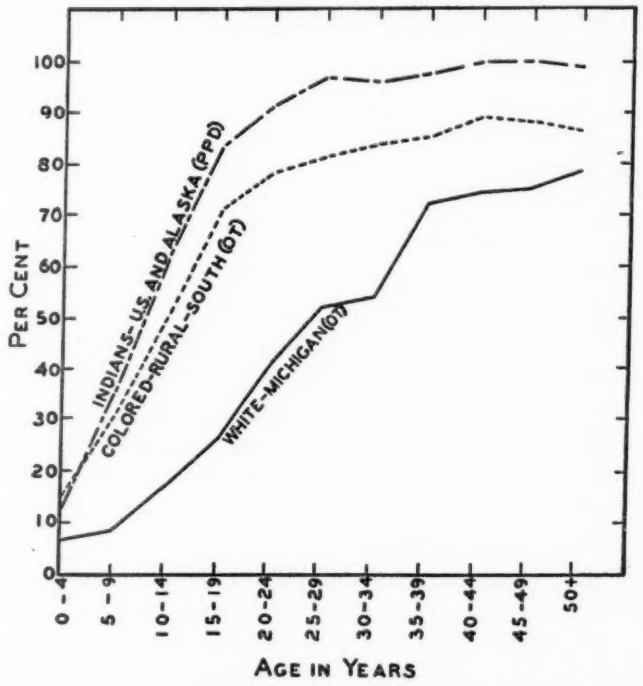

CHART 2. Incidence of tuberculous infection in some areas of the United States and Alaska.

It will be observed that the curve representing the incidence of tuberculous infection rises more rapidly among the Indians than among the colored and much more rapidly than among white persons in rural areas.

That the incidence of tuberculous infection is associated with living conditions was demonstrated in a survey conducted among the Sioux Indians on the Rosebud Agency. Here it was found that 79 per cent of Indian children attending government and mission schools reacted to

tuberculin in contrast to 32 per cent of Indian children attending the county public schools. The children attending the county schools came from more or less widely separated ranches where living conditions were more or less comparable to the white population, while those attending the government and mission schools came from the crowded, poorly housed families living under conditions which would compare with an urban slum. Similarly, in Metlakatla, Alaska, where housing conditions are good, only 2 per cent of preschool children were tuberculin-positive.

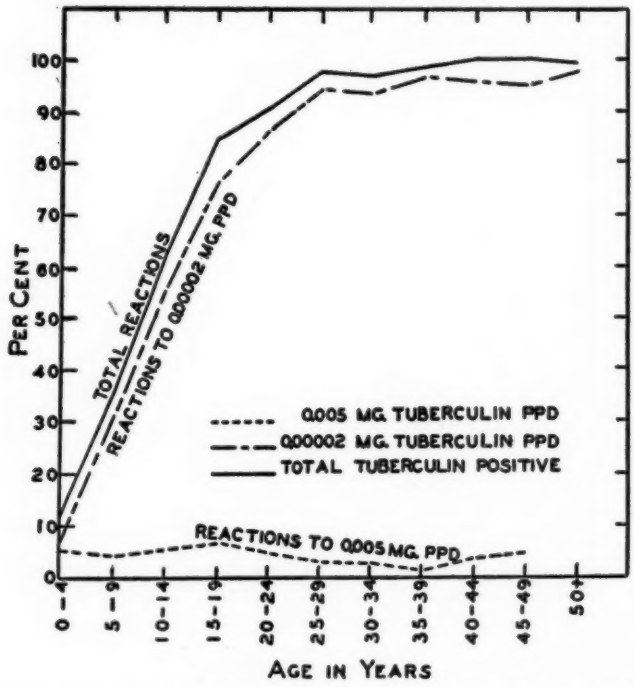

CHART 3. Incidence of tuberculin reaction among Indians, by age and dosage.

This was in striking contrast to 24 per cent reactors among the same age group in Hoonah, Alaska, where many families live together in large clan houses. Among children five to nine years of age, 70 per cent were positive in Hoonah and only 30 per cent in Metlakatla, while among those ten to fourteen years of age, 93 per cent in Hoonah and 58 per cent in Metlakatla reacted.

The percentage of all Indians examined who reacted to the two doses of tuberculin is presented in five-year age periods in chart 3.

From this chart it will be observed that approximately 95 per cent of the Indians who reacted to the intracutaneous injection of tuberculin reacted to 0.000,02 mg. of Purified Protein Derivative tuberculin and that the percentage of positive reactors increased rapidly with increasing age. On the other hand, of the approximate 5 per cent who reacted to the second dose of 0.005 mg. PPD, no correlation to the age of those tested was observed. These observations parallel those noted by one of us (J.D.A.) in a similar study among colored persons. In a previous publication attention was called to the fact that a larger percentage of Indians than white persons reacted to the first dose of Old Tuberculin and that the reaction to this dose was more intense.

The incidence of pulmonary tuberculosis among some of the Indian tribes was determined by roentgenological examination of unselected groups of the general population. Among the 8,072 Sioux Indians living on the Pine Ridge Agency, South Dakota, roentgenologically demonstrable pulmonary tuberculous lesions of clinical significance were observed in 6.1 per cent of 6,325 who were X-rayed by local agency and special tuberculosis physicians of the Indian Service not assigned to the BCG study group, while among the 7,994 Sioux Indians of the Rosebud Agency, South Dakota, 2,450 were X-rayed and clinically significant lesions were noted in 3.1 per cent. Of the 1,026 Shoshones and 1,164 Arapahoes living in Wyoming, 574 and 740 of each tribe, respectively, were X-rayed and significant lesions were noted in 5.7 per cent of the Shoshones and among 5.8 per cent of the Arapahoes. Of the 4,841 Indians living on the Pima Agency, Arizona, 2,060 were X-rayed and clinically significant lesions were observed in 1.1 per cent. Of the estimated 5,000 Indians living in the villages of southeastern Alaska, 3,897 have been x-rayed, 6.9 per cent of whom showed pulmonary lesions of clinical significance. Dahlstrom has examined roentgenologically 60 per cent of the Apache Indians at Fort Apache Agency, Arizona, 24 per cent of the Apaches at San Carlos Agency, Arizona, 34 per cent of the Apache Indians at Mescalero Agency, New Mexico, and 73 per cent of the Apache Indians at Jicarilla Agency, New Mexico. Clinically significant lesions were found in 2.4 per cent at Fort Apache, in 1.3 per cent at San Carlos, in 2.1 per cent of those examined at Mescalero and in 2.4 per cent of those examined at Jicarilla. The X-ray field program has been greatly facilitated by the use of a truck equipped with a portable X-ray machine and a motor generator so that pictures can be taken anywhere and at any time. A portable collapsible tent is used for a dark room, and

oftentimes plates are developed on the spot. Without the free use of the airplane, the Alaskan studies could not have been carried on.

The results of these studies, on representative cross-sections of different Indian Agencies, lead us to the conclusion that, while the incidence of tuberculous infection and disease is high among the Indian population, the Indian as a race is not peculiarly susceptible to tuberculosis and that the character of the tuberculous lesions, as determined roentgenologically, is not significantly different from that observed among the white population. The high rate of tuberculous infection and disease among Indians may be attributed, at least in part, to social and bionomic factors. That similar factors play a rôle among the white population has been definitely shown by Edwards in his case-finding survey in New York City. Of a total of 133,062 persons X-rayed, the incidence of active tuberculosis varied from 0.4 per cent among high school students to 5.3 per cent among transients and homeless persons.

When active cases of tuberculosis are found, every effort is made by the physicians and field nurses to arrange for hospitalization in one of the Service sanatoria or at an institution under contract. During the last fiscal year 4,793 Indian cases were treated in the tuberculosis sanatoria and general hospitals of the Service.

These field surveys have been of tremendous value in awakening interest and stimulating a desire for treatment, as well as giving a true picture of the tuberculosis problem in the Indian population. The waiting lists for admissions are longer, as is the length of stay in the hospitals. A program of health education in the hospitals makes it possible for Indian patients to acquire knowledge of the treatment and prevention of tuberculosis which makes them more conversant along these lines than the average lay person in their communities.

Evaluation of Calmette-Guérin Vaccine (BCG)

The protective value of BCG vaccine against tuberculosis in man has not been definitely established, since the results claimed for the vaccine lack uniformity and, in most instances, the studies have not been properly controlled.

In order to obtain more precise information on the protective value of BCG vaccine the present study was undertaken, under carefully controlled conditions, on a population in its natural habitat, without in any way modifying the mode of living or the degree of exposure to existing

cases of tuberculosis. A committee consisting of Drs. Esmond Long, Kendall Emerson and William Charles White gave their approval to the undertaking.

From February, 1936 to February, 1938, 1,565 persons ranging in age from one to 19 years were vaccinated intracutaneously with BCG vaccine. During the same time, 1,459 persons of the same age and sex, living in the same area and under precisely the same conditions, were injected with 0.1 cc. of sterile physiological salt solution and served as controls. Before their inclusion in this study both the vaccinated and control groups had failed to react to the intracutaneous injection of both 0.000,02 and 0.005 mg. of Purified Protein Derivative tuberculin. With few exceptions the chests of the members of both groups were X-rayed either shortly before or shortly after they were tested with tuberculin.

This study was conducted on different tribes of American Indians of varying degree of blood admixture, living on the Pima Agency, Arizona, the Wind River Agency, Wyoming, the Turtle Mountain Agency, North Dakota, the Rosebud Agency, South Dakota, and Indians living in southeastern Alaska. These Indians living under widely different climatic conditions were for the most part indigenous to their present locality, and those included in this study remained in their localities except for a very few who migrated elsewhere. While they varied widely in their physical characteristics, dietary habits, social and economic patterns, their economic level is uniformly low.

That intensive follow-up of both vaccinated and control groups has been carried out is indicated by the fact that approximately 95 per cent of both of these groups have been reëxamined annually for the past three years. This is to be attributed to the efficiency and interest of the field nurses of the Indian Service, as well as to the coöperation of the Indian population. During the interval between annual examinations the field nurses see the BCG vaccinated and control cases at approximately monthly intervals and note the occurrence of any significant illness which may have occurred since their last visit, as well as arrange for X-ray examination of any case that presents symptoms suggestive of tuberculosis.

The avirulence of the BCG culture used for preparing the vaccine has been determined at irregular intervals by injecting 30 mg. of the culture intraperitoneally into guinea pigs. One of us (J. D. A.) has had the

same culture under observation for over twelve years, and thus far has not observed any indication of any increase in the virulence of the culture.

The BCG vaccine used in this study was prepared as required at each Agency, great care being taken to prevent contamination with virulent tubercle bacilli. The vaccine was used within three days, although most of the injections were made within the first twelve hours. The vaccine in amounts of either 0.1 or 0.15 mg. was injected into the skin over the region of the deltoid. The site of the injection was examined forty-eight hours after to determine the character of the immediate reaction and was subsequently examined at weekly intervals until healing was completed.

In no instance did we observe any untoward local or general reaction and in no instance was surgical intervention necessary. In about 5 per cent of cases the regional axillary lymph nodes were palpable but did not ulcerate.

The vaccinated and control cases were tuberculin tested and roentgenographed at yearly intervals. The films were interpreted without any knowledge of the tuberculin reaction nor of the group to which the case belonged. Those showing roentgenological lesions of a doubtful character have been reviewed by different members of the staff of the Henry Phipps Institute, to whom we express our appreciation. Roentgenologically demonstrable pulmonary lesions of doubtful significance have not been included as tuberculous; the final diagnosis has been postponed until films taken at varying intervals may make it possible to arrive at a definite diagnosis.

The results of the tuberculin test and roentgenological examinations are presented for one, two and three years following vaccination in table 1.

It will be observed from this table that approximately 95 per cent were retested with tuberculin and roentgenographed annually during the three years of observation. The incidence of positive tuberculin reactions among those vaccinated with BCG has remained practically the same during this period of time, while there has been a definite and constant increase of infection among the control group, as indicated by the increment of those who have become tuberculin-positive over the same period of time.

Among those vaccinated with BCG one year previously, roentgenologically demonstrable primary lesions of tuberculosis were observed

in 2 females aged four and eleven, respectively. Among the control cases tuberculous lesions were observed in 18 cases. In 15 instances there was observed definite enlargement of the hilar nodes, in one moderately advanced tuberculosis, one miliary tuberculosis, while in one instance there was noted definite scanty pulmonary infiltration with

TABLE 1

Effect of BCG vaccination among some Indians of the United States and Alaska

	GROUP							
	BCG				Control			
Number of cases, total, all ages..	1,565				1,459			
	Tested		Positive		Tested		Positive	
	Number	Per cent	Per cent		Number	Per cent	Per cent	
Tuberculin Reaction:								
1 year later	1,483	94.7	93.3		1,311	89.8	12.7	
2 years later	1,449	92.6	93.4		1,355	92.9	18.5	
3 years later	1,459	93.3	92.5		1,360	93.2	24.6	
	X-rayed		Tuberculous Lesions		X-rayed		Tuberculous Lesions	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Roentgenological Examination:								
1 year later	1,509	96.4	2	0.13	1,399	95.9	18	1.3
2 years later	1,497	95.7	5	0.33	1,383	94.8	40	2.9
3 years later	1,482	94.6	6	0.40	1,376	94.3	59	4.3
Deaths—Tuberculous:								
1 year later	1	0.06			3	0.21		
2 years later	1	0.06			6	0.41		
3 years later	3	0.18			11	0.75		
Deaths—Nontuberculous:								
1 year later	10	0.64			7	0.48		
2 years later	13	0.83			13	0.89		
3 years later	19	1.2			20	1.3		

subsequent calcification of the hilar nodes. Among the BCG vaccinated cases one death from tuberculosis occurred during the first year. This occurred in a thirteen year old male who, forty-eight hours following the intracutaneous injection of the vaccine, showed a definite Koch phenomenon, indicating that infection had occurred previous to vaccination, and who died three months later from tuberculous meningitis

confirmed by demonstration of tubercle bacilli. In view of the fact that a period of five weeks elapsed between the time that the tuberculin test was performed and vaccination was carried out, there exists the possibility that in this instance the negative tuberculin reaction may have been due to a preallergic state or that infection with virulent tubercle bacilli occurred in the interval between the tuberculin test and vaccination.

In the control group, 3 deaths from tuberculosis occurred; 2 females, aged eight and seventeen, respectively, died from miliary tuberculosis confirmed by X-ray, and a male, aged two, from tuberculosis of a knee and pulmonary tuberculosis. In the BCG vaccinated group 10 deaths were attributed to nontuberculous causes. Among the control group, 7 deaths occurred from nontuberculous causes.

It is noteworthy to observe that among the control group the tuberculin reaction showed a definite increase with increasing age, while the percentage of roentgenologically demonstrable lesions decreased with increasing age. Among the BCG vaccinated cases the tuberculin reaction was not affected by age, while the number of tuberculous lesions were too few to be statistically significant by age.

During the second year approximately the same number of cases were X-rayed and tuberculin tested as during the first year. The percentage of BCG vaccinated cases who reacted to tuberculin was the same as in the preceding year, while among the controls the percentage of positive tuberculin reactions had increased from 12.7 per cent to 18.5 per cent. Among the vaccinated cases primary tuberculous lesions were observed in 3 additional cases, making a total of 5 cases for the two years. It is significant that 4 of the cases were in females. Among the control group tuberculous lesions were observed in 22 new cases, making a total of 40 cases for the two years of observation. Of the 15 males who had roentgenologically demonstrable lesions, 11 had a primary lesion, 3 minimal tuberculosis and one Pott's disease, while among the 25 females, 23 had a primary lesion, one minimal and one moderately advanced tuberculosis. No additional deaths from tuberculosis occurred among the vaccinated group, while 3 additional deaths occurred among the control group. Two were diagnosed as miliary tuberculosis, while one died from moderately advanced tuberculosis and tuberculous meningitis. Among the vaccinated group, 3 additional deaths from nontuberculous causes occurred. Among the control group there occurred 6 additional deaths from nontuberculous causes.

Tabulations just completed at the end of three years show one addi-

tional case of tuberculosis developing in the vaccinated group and 19 additional cases in the controls. Thus, for the entire three-year period, ten times more tuberculosis cases are reported in the control group than in the vaccinated group.

Two additional deaths from tuberculosis in the vaccinated group bring the total deaths to 3, and 5 more deaths in the control group give a total of 11 for the three-year period. The percentage of deaths from nontuberculous causes remains the same in both groups.

SUMMARY

1. The incidence of tuberculous infection and disease was determined by means of the intracutaneous tuberculin test and roentgenological examination on representative cross-sections of Indian population living in different areas of the United States and Alaska.

2. The high incidence of infection and disease may be attributed to social and bionomic factors.

3. The character of tuberculous lesions determined roentgenologically is not significantly different from that observed among the white population.

4. The intracutaneous injection of BCG vaccine is a relatively innocuous procedure, resulting in a local lesion at the site of injection, uncomplicated by any general reaction.

5. The results obtained thus far indicate that both the morbidity and mortality from tuberculosis are significantly lower among those vaccinated with BCG vaccine than among the unvaccinated control group. No definite conclusion should be drawn at this time as to the protective value of the vaccine. Continued observation will be necessary for a long period of time before final evaluation is possible.

SUMARIO

1. En típicos grupos de indios que viven en diversas partes de los Estados Unidos y de Alaska, se determinaron los coeficientes de infección y enfermedad tuberculosa por medio de la intracutirreacción a la tuberculina y el examen roentgenológico.

2. Los elevados coeficientes de infección y de enfermedad pueden imputarse a factores sociales y bionómicos.

3. La naturaleza de las lesiones tuberculosas determinadas roentgenológicamente en los indios no discrepan mayor cosa de las observadas entre la población blanca.

4. La inyección intracutánea de BCG constituye un procedimiento relativamente inocuo que produce una lesión local en el sitio de la inyección, y sin que la complique ninguna reacción general.

5. Los resultados obtenidos hasta ahora indican que tanto la morbidad como la mortalidad tuberculosa son mucho menores entre los vacunados con BCG que entre los testigos sin vacunar. Por ahora no debe sacarse ninguna conclusión precisa en cuanto al valor protector de la vacuna, y será necesario continuar la observación por un período prolongado antes de poder formular una evaluación definitiva.

TUBERCULOSIS IN THE NEGRO[1]

VICTOR F. CULLEN[2] AND REUBEN HOFFMAN[3]

The literature concerning tuberculosis in the Negro is voluminous and contradictory. Opinions as different as the color of the two races under discussion are encountered and these opinions may be based on work as far apart as are careful postmortem examinations and pure speculation. However, one general group of facts seems to be fairly well agreed upon: given an environment predisposing to tuberculosis, the Negro will show manifest disease earlier, the disease will run a shorter and more violent course and will end fatally more frequently than in the white.

The facts are accepted, but the answer to the how and why is disputed. Some investigators hold that there is a fundamental, biological difference between the two races accounting for the difference in the incidence and in the outcome of the disease. Pinner and Kaspar (1) state that the "Discrepancies observed lead necessarily to the conclusion that infection tends to produce a high state of allergy in the Negro, but that he, unlike the white, does not readily acquire a state of increased resistance coincidentally." They acknowledge the importance of environmental conditions, but do not admit that they offer a complete explanation for the differences noted in the two races. They conclude with the statement that "We are impressed by the necessity of considering the likelihood of true genotypic differences between the two races in order to explain their different reactions to tuberculosis. . . ." Other investigators (2) maintain that the Negro's lack of resistance to tuberculosis is not a racial factor, but is due entirely to his environment. Still others (3) maintain that they see no difference at all between the white and Negro in their reaction to tuberculosis.

Daily observations of the tuberculous Negro over a period of years leaves us with the definite opinion that his resistance to tuberculosis is

[1] Presented before the Medical Section at the 37th annual meeting of the National Tuberculosis Association, San Antonio, Texas, May 5, 1941.

[2] Maryland Tuberculosis Sanatorium, State Sanatorium, Maryland.

[3] Maryland Tuberculosis Sanatorium (Colored), Henryton, Maryland.

somewhat lower than the white, but that this fact is due almost solely to such extrinsic factors as physical environment, mental attitude and inadequate facilities for hospitalization and treatment. In our opinion a genotypic racial factor, if any exists, plays a minor rôle.

The question as to whether or not the Negro evidences a racial lack of resistance must therefore remain a controversial, and for the present, unanswered question. There is, however, nothing controversial about the part the Negro's socio-economic status plays in modeling the course of his disease. Roth (4) writes, "The poverty of the Negro population as a whole guarantees that the quality and quantity of its diet will be inferior, that it will live in crowded districts in poorly constructed homes with multiple opportunities for the dissemination of the disease from infected to noninfected individuals, and that a large proportion of the wage earners will be employed in industries known to be relatively predisposing to tuberculosis." This describes accurately the status of the Negro and needs no amplification.

Another factor that militates against the Negro is his mental attitude toward illness. Those who deal with the sick Negro are frequently amazed at the disregard he shows for his state of health. To have him ignore such symptoms as fatigue, protracted cough, loss of weight, dyspnoea and even blood spitting is far from uncommon. The average Negro gives one the impression of being an optimist, and when optimism is palpably untenable, a serene fatalist. His optimism is evidenced by the belief that the symptoms of illness from which he suffers are of passing significance and will improve as time goes on. He will without undue concern tolerate symptoms that would have sent the average white to a doctor long since. In addition, he has an abiding faith in medicines and is a willing victim of all the advertised cures for whatever ails him.

On questioning the patients who enter our institution in a far advanced stage of the disease one receives a variety of answers, the most frequent being that they felt something was wrong, but postponed seeking medical advice pending that improvement in their condition which they were reasonably sure would come about. Usually, it was not until symptoms became alarming that medical care was sought.

Walsh and Pool (5) in writing about Negroes say, "When we look into the matter we shall find that the occurrence of what the profession calls 'organic' disease is much higher in the Negro than in the white. Not only are such misfortunes more common, but they are met in a more

advanced stage. . . . This disparity is due to the habitual disregard which the Negro displays toward all form of disease. We may then assume that only those diseases tend to appear among the Negroes which are impervious to human disregard—diseases against which emotional defenses are inadequate."

Of much more significance, however, in explaining the picture of tuberculosis in the Negro is the inadequacy of hospital beds and facilities for treatment so strongly brought out in the study made by the National Tuberculosis Association in 1934 (6). The situation has admittedly somewhat improved since then, but not enough to invalidate the facts nor the obvious conclusions to be drawn from them.

During the period covered by that study there were about 21,099 deaths each year from tuberculosis among Negroes throughout the country with a total available bed capacity of 3,334 or 16 beds for each 100 deaths. On the basis of the minimum and admittedly too low requirement of one per annual death only one out of 6 of the admitted Negro sufferers from tuberculosis could be hospitalized. In the thirteen southern states, where two-thirds of the nation's Negro population lives, a still more serious condition existed. In this area, in the same period, there were 12,000 annual deaths from tuberculosis among Negroes and the number of available beds was 1,666, or 14 for each 100 deaths. In one state 216 of the 218 beds were limited to the residents of 4 counties, leaving 2 beds for the remaining 91 counties. Along with this lack of beds was the equally serious problem of the general lack of medical care. In one of the larger southern states 23 per cent of all Negroes dying (violent and accidental deaths excluded) died without medical care.

Some observers (7) have advanced the theory that the Negro has a lower sensitivity to pain and that, since tuberculosis is a relatively painless disease, it can progress to a far advanced stage before the Negro becomes aware of it. We have no belief in such a theory; much rather would we say that the Negro exhibits a disregard for moderate pain in the belief that pain is a necessary evil associated with illness. The numerous complaints about pain and the numerous pain relieving drugs on the shelves of our pharmacy belie any belief on our part in an altered nerve mechanism.

Tuberculosis in Negro children deserves special emphasis since the incidence and subsequent course of the disease is so obviously governed by their environment and because of the fact that the greatest disparity

between tuberculosis in the white and Negro is manifested in Negro children.

Eighty per cent of our Negro children in the sanatorium show the usual picture of first-infection tuberculosis, but differ from white children in several respects: a greater amount of extrapulmonary tuberculosis, particularly suppurative adenitis, and a greater involvement, sometimes massive, of the tracheobronchial lymph nodes. Despite these differences, these children do nearly as well as the white.

However, we are confronted in the remaining 20 per cent with an extremely serious and totally different situation, the high incidence of the adult (reinfection) type of pulmonary tuberculosis. Whereas reinfection pulmonary tuberculosis is relatively rare in white children, it is relatively common among Negro children. One out of every 5 Negro children admitted to the sanatorium has the reinfection type of pulmonary tuberculosis and 98 per cent of these have positive sputa or positive gastric washings.

The generally unwholesome conditions of their surroundings, the too frequent negligence of the adult with the open case of tuberculosis in the home with whom they live in intimate contact (and with whom they frequently share the same bed), the multiple opportunities for exposure, often massive, and the frequent inability of either the adult or the child to receive hospitalization seem adequately to account for the picture of serious pulmonary disease as we encounter it in them.

We cannot agree to any theory which explains this high incidence and fatal outcome of tuberculosis in the Negro on grounds of racial susceptibility or racial lack of resistance. If white children living in the same environment, and exposed to the open case in the same manner, and faced with the same difficulties in getting hospitalized were found to still maintain their present favorable advantages over the Negro children, then we would be willing to admit that they possess a superior racial resistance.

The death rate in the group of Negro children suffering from the adult type of pulmonary tuberculosis is appallingly high when treated conservatively, but when given collapse therapy, they do surprisingly well. They tolerate surgical procedures better than do Negro adults and a majority of those treated ultimately get good results.

Excluding thoracoplasties from consideration, we have no age limit for Negro children below which collapse procedures are contraindicated. The type of lesion and not the age of the patient determines

the choice of the procedure. Of the operations performed in our sanatorium, 8 per cent of the thoracoplasties were in the juvenile group (the youngest patient being nine years of age), 9 per cent of the phrenic nerve surgery was performed on juveniles (the youngest being six years), 15 per cent of the closed pneumonolysis (the youngest being six years).

Our experience with collapse therapy in Negro children contradicts the observation that reinfection pulmonary tuberculosis in Negro children with positive sputa is a 100 per cent fatal disease and that their life expectancy is two years (8).

The response of the Negro in general to collapse therapy is also a disputed subject with the majority of the opinions (9, 10) expressing the belief that Negroes respond much less favorably than do whites. Our experience, on the contrary, is that, when collapse therapy is indicated and performed, the results are nearly as good as in the white race.

Experience with collapse therapy in the Negro has crystallized several definite beliefs. Delays are dangerous and halfway measures are not to be employed. A prolonged period of rest to observe the progress of a lesion so seldom accomplishes any good that it is seldom worth employing. Collapse therapy offers a greater chance for success in the Negro than any other procedure and should be employed as widely as possible.

Extensive use has been made of pneumothorax as a collapse measure. In a previous communication (11) it was pointed out that complete obliteration of the pleural space (or adhesions so wide-spread that only insignificant collapse was obtained) occurred in 26 per cent of the patients and that adhesions prevented a satisfactory collapse in 62 per cent. Therefore most pneumothoraces are ineffectual as the result of adhesions. An early attempt should be made to sever adhesions and, as a principle, the only indication for the performance of a thoracoscopic examination is adhesions preventing an adequate collapse; and the only requirement is sufficient room for the safe manipulation of the instruments. Thoracoscopic examinations (with or without the severance of adhesions) were performed 132 times on 109 Negroes. They have shown that this procedure carries far less danger than the maintenance of an inadequate pneumothorax. Ample opportunity to compare pneumothorax with and without facilities for pneumonolysis has shown that pneumothorax, unaided by supplementary procedures, with pneumonolysis as the procedure of choice, is an inadequate measure in the treatment of pulmonary tuberculosis in the Negro. Here we have an example

where the expression "half-way measures have no place" takes on meaning: pneumothorax without pneumonolysis, when indicated, is decidedly a half-way measure.

Operations on the phrenic nerve were performed 110 times. Phrenic nerve surgery has been chiefly employed for basal lesions and as a supplementary procedure to pneumothorax therapy (other procedures being contraindicated). In a selected number of cases, on the other hand, it has been used with the full knowledge that there was everything to gain and nothing to lose. In these latter cases, with a few notable exceptions, results have been poor. Used as a supplementary procedure, the results were varied but, on the whole, rather disappointing. Phrenic nerve surgery in the Negro seems to carry the same degree of unpredictability and disappointment as in the white.

Thoracoplasties were done on 50 patients with a total of 112 stages. Nine deaths occurred in this group. Four were surgical deaths, that is, deaths occurring while on the surgical service and resulting directly from operative interference. Two were delayed, caused by progression of postoperative spreads. Two were due to cardiac failure, one occurring two weeks after operation and one occurring three months after operation. One followed a blood transfusion where the blood was incompatible. This gives an operative death rate of 8 per cent and a delayed rate of 12 per cent. There was conversion of the sputum in 60 per cent of the completed thoracoplasty cases.

There is only one difference between the white and the Negro, when surgery is considered, that we wish to emphasize. The Negro is sicker and usually has more extensive disease. His prognosis is admittedly poorer. There is all the more reason, therefore, when considering collapse therapy in the Negro, to widen the scope of the indications for performing these measures. An increase in the surgical death rate will in all probability follow, but that is of statistical importance only, since the death will certainly occur medically. Everything to gain and nothing to lose may sound very prosaic and unscientific, but both the physician and surgeon will be rewarded with an increased number of live patients.

DISCUSSION

The purpose of this communication is to elaborate a few general principles of the truth of which we have become convinced as a result of our daily study and treatment of the tuberculous Negro. Regardless of the reasons for the high prevalence and increased mortality from

tuberculosis in the Negro, the sure path to the reduction of both is in the improvement in his standard of living and an increase in the number of available beds for the treatment of tuberculosis. No national program for the control and eradication of tuberculosis can hope to be successful unless the opportunities for hospitalization and facilities for treatment are available equally to Negroes and to whites. The Negro's response to treatment will closely approximate that in the white, but he must be given the chance to prove this. The campaign against tuberculosis is doomed to disappointment and failure if we continue to consider the Negro as a poor prospect for improvement and allow this attitude to affect our judgment as to whether or not an intensive campaign of economic betterment, health propaganda and adequate facilities for hospitalization should be carried out.

The source of the opinions expressed and the results offered in this communication is the colored branch of the Maryland Tuberculosis Sanatoria, more commonly known as the Henryton Sanatorium. Henryton is a state-owned and state-maintained sanatorium of 490 beds devoted entirely to Negro patients. It had its beginning in 1923 as a 60-bed unit. It accepts all types of tuberculosis and all ages, with the one exception that the number of beds available for Negro children under three years of age is sharply limited. Its beds are open to any legal resident of the state.

The nursing personnel, with the exception of a few white supervisors, is Negro. A training school for nurses is maintained by the sanatorium. Half of the medical staff is colored. All lay help, with the exception of a few semiskilled laborers, is Negro.

All the surgery, with the exception of thoracoplasties, is performed at the sanatorium. The thoracoplasties are done at the surgical unit of one of the near-by white sanatoria with additional beds for the patients from Baltimore available at Baltimore City Hospitals and Johns Hopkins Hospital in Baltimore. It carries a full complement of consultants. A working agreement with Johns Hopkins Hospital has resulted in the establishment of a consultant obstetrical service with the deliveries done at that hospital.

Negroes in Maryland represent 17 per cent of the population and account for 46 per cent of the deaths from tuberculosis. For 1939 the death rate per 100,000 from tuberculosis was 41.6 for whites and 172.9 for Negroes.

The total number of beds available in the state of Maryland for the tuberculous Negro brings the ratio of beds per annual death to 1.25.

CONCLUSIONS

Briefly considered, the Negro is subjected to an environment that predisposes him to tuberculosis and that diminishes his chance of cure once he has contracted it. In the vast majority of cases he goes unhospitalized because beds are not available. He has a philosophy of life, some aspects of which might well be imitated, but which under his circumstances does him more harm than good.

It is questionable whether we should allow ourselves to speculate about the racial factor about which, at best, only indefinite conclusions can be drawn, when we cannot or have not studied and observed the effect which economic opportunities and hospital facilities equal to those enjoyed by the white would have on the incidence and mortality of tuberculosis among Negroes.

CONCLUSIONES

En resumen, el negro está expuesto a un ambiente que lo predispone a la tuberculosis, y que aminora sus probabilidades de curación una vez que ha contraído el mal. En la inmensa mayoría de los casos no se hospitaliza por no haber camas para ello. El negro posee una filosofía de la vida, algunos de cuyos aspectos son dignos de imitación, pero que en las circunstancias actuales le hacen más mal que bien.

Es dudoso que debamos teorizar acerca del factor étnico con respecto al cual, cuando más, sólo podemos sacar conclusiones imprecisas, visto que no podemos estudiar o no hemos estudiado y observado el efecto que ejercería sobre la frecuencia y mortalidad de la tuberculosis en los negros la utilización de oportunidades económicas y medios hospitalarios iguales a aquéllos con que cuenta el blanco.

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THE MORTALITY FROM TUBERCULOSIS AMONG THE RACE STOCKS IN THE SOUTHWEST[1]

LOUIS I. DUBLIN[2]

Over a period of years, I have been calling attention to the fact that tuberculosis in our country is approaching the residual stage. There can no longer be any question but that this disease is coming under control, or, as Homer Folks likes to put it, can be virtually eliminated as a factor in mortality in America. How long this will take to accomplish will depend on how vigorously we concentrate our attack on those areas and groups of people among whom the disease still flourishes. For, in various parts of the country, there are areas and groups, both large and small, among whom the control of tuberculosis is still in a very rudimentary state. I propose, in this paper, to direct your attention to this particular problem. This is all the more appropriate on this occasion, when we are meeting in the Southwest, which contains more than its share of such groups.

A glance at the tuberculosis map of the United States (figure 1) shows clearly that every state in the Southwestern section of the country has a mortality rate from tuberculosis well above the average for the country as a whole (table 1). This condition characterizes our whole Southern border section from the Atlantic to the Pacific, but it is worst west of the Mississippi River. The two states with the highest rates in the country are there, namely, Arizona (180.9 per 100,000 in 1939) and New Mexico (82.2 per 100,000). Texas has a death rate (61.4) considerably higher than the average for the country (47.2) and in Louisiana and California the rates (59.1 and 57.6 respectively) are not much lower than that in Texas.

This condition is not associated with adverse meteorological conditions. On the contrary, we know that the climate is generally salubrious. Large numbers of patients from all over the country have made most of these states a favorite curing place. Philanthropic and church groups and

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clinicians have picked out these areas for the establishment of excellent tuberculosis sanatoria. Large numbers of ex-patients have settled in these states and, in fact, have helped to build them up. But these facilities, in a good part of this area, have been built up for nonresidents who are seeking health there, while the local problem of tuberulosis and the facilities for its care have been largely neglected. For, over and above the high rates from tuberculosis in these states as a result of the heavy concentration of nonresident patients, there is the presence of

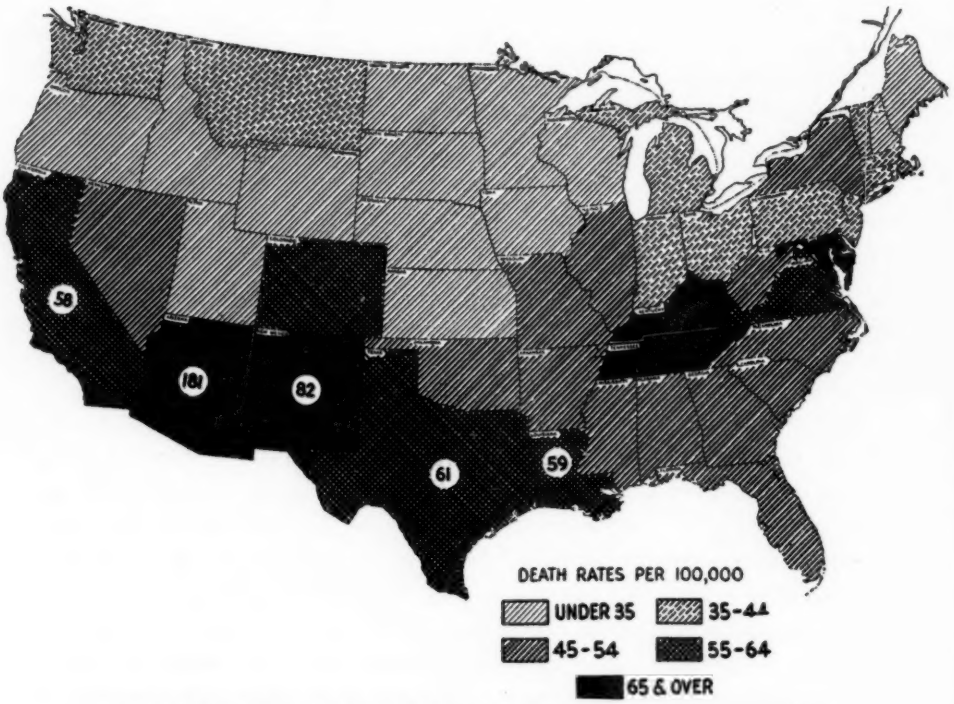

FIG. 1. Mortality from tuberculosis in the United States, total persons, 1939

large numbers of native race stocks which suffer abnormally high rates from tuberculosis.

The pattern with respect to these race stocks is not uniform throughout the area. In Louisiana it is the Negro who makes the state mortality rate high. In Texas, it is the Negro and the Mexican. In New Mexico, it is predominantly the Mexican who is responsible for the high rate among residents of the state, but with a sizable Indian admixture; in Arizona, likewise, the Mexican, but also a very sizable Indian group, the

largest number of *full blooded* Indians of any state of the country. Finally, in California, the resident tuberculosis problem is concentrated chiefly among the Mexicans, but there are also sizable numbers of Chinese, Japanese and Filipinos, among whom the disease is wide-spread.

Our knowledge of the nature and extent of tuberculous disease among these peoples in our Southwest has been seriously hampered by our ignorance of their actual numbers in various localities and of the number of deaths from tuberculosis among them. This is particularly true of our so-called Mexican contingent. The Federal Government has given up the task of identifying them in Census returns and in the collection of vital statistics, but fortunately some of the state and local officials who have to deal with the problem have attempted to keep count of the numbers and mortality among Spanish-speaking persons and their offspring. It is readily understandable that these peoples do not wish to be considered anything but our fellow countrymen, and they particularly resent any designation which separates them from other whites; but if we are to know and deal with health problems among them, we must be realistic in at least recording and analyzing their vital statistics. That necessarily involves some means of estimating their numbers or identifying them, and certainly of identifying them in medical and mortality records. Despite the difficulties involved, there is a body of information available with regard to the mortality from tuberculosis in the various race stocks of the Southwest. For much of this material I am indebted to state and local health officers and registrars who have been good enough to furnish me recent and unpublished data on mortality in the racial groups in which we are interested. Since in many cases I have had to estimate populations, the death rates used may be subject to slight correction later, when census data become available.

TUBERCULOSIS MORTALITY AMONG NEGROES IN THE SOUTHWEST

Of these states in the Southwest, the highest proportion of Negroes is found in Louisiana where they constitute 37 per cent of the population. In Texas, the proportion is 15 per cent for the state, but the Negro population is concentrated in the eastern part of the state where it constitutes approximately one-fourth of the whole population. California's Negro population is appreciable in the aggregate, but it is definitely concentrated in a few cities, particularly Los Angeles.

In the Southwest, the problem of Negro mortality is pretty much of a piece with that elsewhere in the country. In the North and Midwest,

the mortality from the disease in Negroes is on a par with that in the South and in some spots it is much worse. But the dimensions of the problem are much smaller in the North. In Louisiana, the death rate

TABLE 1

*Death rates from tuberculosis, all forms, per 100,000 population, United States, 1939**

STATE	DEATH RATE	STATE	DEATH RATE
United States	47.2	South Atlantic (*cont'd*)	
		Virginia	61.1
New England		West Virginia	46.7
Maine	33.4	North Carolina	51.1
New Hampshire	28.5	South Carolina	44.9
Vermont	38.3	Georgia	48.8
Massachusetts	38.2	Florida	50.0
Rhode Island	37.7		
Connecticut	35.2	East South Central	
		Kentucky	70.7
Middle Atlantic		Tennessee	80.5
New York	48.7	Alabama	54.9
New Jersey	43.3	Mississippi	49.8
Pennsylvania	42.9		
		West South Central	
East North Central		Arkansas	51.2
Ohio	42.7	Louisiana	59.1
Indiana	41.5	Oklahoma	46.1
Illinois	46.2	Texas	61.4
Michigan	36.9		
Wisconsin	27.7	Mountain	
		Montana	44.9
West North Central		Idaho	19.1
Minnesota	29.2	Wyoming	22.4
Iowa	19.2	Colorado	59.8
Missouri	47.0	New Mexico	82.2
North Dakota	22.1	Arizona	180.9
South Dakota	29.4	Utah	17.4
Nebraska	16.6	Nevada	54.2
Kansas	23.1		
		Pacific	
South Atlantic		Washington	41.5
Delaware	58.6	Oregon	30.0
Maryland	72.2	California	57.6
District of Columbia	64.5		

* Data prepared by United States Bureau of the Census.

from tuberculosis among Negroes in 1937–1939 was 102.5 per 100,000, as compared with 38.0 for whites. In Texas, state figures for the same years show a rate of 92.2 per 100,000 among Negroes, as compared with

50.5 for whites. In some of the large cities, the contrast is much greater. In Houston, for example, as against a rate of 40 per 100,000 among white persons in this period, the Negro rate, 137.8 per 100,000, was nearly three and one-half times as high. The figures here in San Antonio are of about the same order. In general, as Smith (1) has shown, the tuberculosis problem among Texas Negroes is rather worse in the cities than in the rural areas. The death rate in the counties containing four of the large cities was approximately 25 per cent higher than in the rest of the state. Davis (2) in his regional breakdown of mortality from tuberculosis in Texas has shown that the panhandle region and the adjoining area to the east, where there are relatively few Negroes and Mexicans, have death rates appreciably lower than the eastern section of the state in which the Negro population is concentrated.

The comparatively small Negro population of California had a tuberculosis death rate of 201.9 in 1937–1939, or over four times that among the white population, excluding Mexicans. The greater part of this problem is concentrated in the cities and it is in the hands of relatively few local authorities to organize the necessary measures for control of tuberculosis among Negroes in this state.

In the large, Negroes constitute the last great reservoir of tuberculosis in our country. They are responsible for over one-quarter of all deaths. The Southwest contains approximately 15 per cent of the Negro population of the country and it must bear its share of the work and responsibility for completing this part of the task.

TUBERCULOSIS MORTALITY AMONG MEXICANS IN THE SOUTHWEST

The problem of tuberculosis among Mexicans is largely concentrated along or near the southern border of the four states that adjoin Mexico. There, uniformly, Mexicans constitute a sizable group for whom some special techniques in control are necessary. Again, I may say, the tuberculosis situation is not much different in those parts of the North where there are sizable colonies of Mexicans and other Spanish-speaking peoples as, for example, among Mexicans in Chicago and Detroit and among the Puerto Ricans in New York City. Tuberculosis programs for these groups in the North must be greatly intensified, and it is likely that those who are working with them in the Southwest can teach us a good deal.

Mexicans, according to the Census of 1930, the only one which recognized them as a distinct group, constituted 12 per cent of the population

of Texas, 14 per cent of that of New Mexico, 26 per cent of that of Arizona and 6.5 per cent of that of California. In California, they are largely concentrated in the southern counties of the state near the border and, in this region, they make up almost 10 per cent of the population. The figure for New Mexico apparently is much understated. It is reported that possibly half the population is of pure or mixed Spanish descent.

Data furnished us by Texas authorities show that in 1937–1939 the death rate from tuberculosis in the Mexican population was 117.9 per 100,000, or about 25 per cent higher than among Negroes, but two and one-third times that among the non-Mexican whites. In some of the urban areas, however, the rates are extremely high. One must go back to the beginning of the century to find rates as high as these for the white population of the country as a whole. Here in San Antonio, the tuberculosis death rate among the 90,000 Mexicans is about 300 per 100,000, or more than double the rate for Negroes, and nearly seven times that among non-Mexican whites. Approximately the same ratios hold for Houston. Again, as in the case of the Negroes, the situation is at its worst in the cities. Smith's data (1) for 1929–1937 show that the death rate among Mexicans in the counties with four of the large cities was three-fifths higher than in the rest of the state. But even in these more favorable areas, the mortality in the Mexican population was two and one-half times that of the other white population and nearly one-third higher than in the Negro population. The effect of the high rates among Mexicans is further shown by Davis' (2) regional analysis of the mortality from tuberculosis in the state. The two regions in the southern part of the state, in which the Mexicans are concentrated and comprise a major fraction of the population, had death rates from tuberculosis over twice as high as the eastern region with a high proportion of colored persons and three times as high as the rates in the Northwest and North Central regions of the state.

Data on tuberculosis in the Spanish-American population in New Mexico are least satisfactory. I have already noted the contrast between official census figures for 1930 and the actual state of affairs as to the proportion of persons of pure or mixed Spanish-American origin among inhabitants of New Mexico.

There are two other items that complicate the problem. First, the certification of deaths in New Mexico, so far as statements of cause are concerned, is rather unsatisfactory. In approximately 20 per cent of the deaths, the cause is either not stated or ill-defined. Obviously under

such conditions vital statistics are rather meaningless. The death rate from tuberculosis is distinctly understated. The other complicating fact is that for a long time the state was popular as a tuberculosis resort, although much less so in recent years than formerly. The best index we have of the spread of tuberculosis among the Spanish peoples in New Mexico is, first, the condition in the border counties, where the proportion of persons of Spanish-American stock is highest and where there are few, if any, sanatoria catering to nonresidents. These counties have resident tuberculosis death rates higher than for the state as a whole. A second source of information is Werner's (3) analysis of deaths from tuberculosis among residents of New Mexico. He found that deaths from tuberculosis among Mexicans accounted for over two-thirds of the total deaths from this cause, or appreciably in excess of their proportion of the total population. Werner's figures cannot be translated into death rates because of the wide disparity between the estimates of the proportion of residents of the state who are of Spanish origin.

In Arizona, the tuberculosis death rate among Mexicans in 1937–1939 is reported by the state officials to be 145.8 per 100,000. Unfortunately, we do not have a corresponding rate for other white residents exclusive of the nonresidents who came to Arizona for cure. The state to-day is relatively the most popular in this regard, and this largely accounts for its highest tuberculosis rate in the country. While it is likely that patients with active tuberculosis from outside the state will infect some of the residents, this is only one and probably a minor factor in the high incidence of tuberculosis in Arizona's Mexicans. For, in those counties in which they form a large part of the population, and which are not important centres of treatment of tuberculosis, the death rates from the disease are high.

In California, the death rate among Mexicans in 1937–1939 is reported by her state officials to be 199.9 per 100,000. This rate, which is over four times that in the rest of the white population, is appreciably in excess of that reported in the other states of the Southwest. This, I believe, does not reflect a situation that is worse than in other parts of this region, but rather better recording of cases; for here there is better appreciation of the problem and, consequently, more adequate provision for its diagnosis. Certainly the sanatorium facilities in southern California provided by local authorities are far more abundant than in other parts of the Southwest inhabited by Mexicans, and these facilities are available to her Mexican residents. A second factor in California is the

concentration of Mexicans in cities to a greater degree than elsewhere in the region.

In Los Angeles County, where numerically the problem is largest, Mexican patients account for approximately 20 per cent of all new cases reported and approximately 25 per cent of all the white patients (4). They contribute about one-sixth of the deaths from the disease in this part of the state, although they constitute only one-thirteenth of the population.

The degree to which the Mexican population in southern California is infected with tuberculosis is exemplified by Bogen's study (5), chiefly among young people, in San Bernardino County. There, using only a first dose of PPD, he found that the percentage of positive reactions was two and one-half times as high in the Mexican population as in the white, although the average age of the former was almost a year less.

TUBERCULOSIS MORTALITY AMONG INDIANS IN THE SOUTHWEST

With a few notable exceptions, tuberculosis is especially rife among Indians everywhere, but the large numbers residing in the Southwest make it a problem of particular importance there. The Indian population of three states in this region, Arizona, New Mexico and California, is approximately 100,000, or 30 per cent of the total Indian population of the country. Arizona has the largest number. In 1930 they constituted 10 per cent of the total population of that state. In New Mexico, 7 per cent of the 1930 population was Indian. In California, however, despite their appreciable number, they are but a tiny fraction of the total population of the state. Arizona reports a tuberculosis death rate of 280.5 per 100,000 among her Indians in 1937–1939. In New Mexico, the reported rate is nearly 200 per 100,000, but the general understatement of tuberculosis mortality in the state applies to the Indian population too. It is probably not much different from the mortality among Arizona's Indians. In California, the rate in the same period was 237.6 per 100,000, higher than among any of the minor racial groups in the state.

As an indication of the high rate of tuberculous infection in the Indians of the Southwest is the finding by Long and Hetherington (6) on the Papagos of southern Arizona. Eighty per cent of the 530 Indians, tested with PPD, gave a positive reaction. At ages five to nine, 62 per cent were positive; at ten to fourteen, 76 per cent; at fifteen to nineteen, 75 per cent; but past age twenty, practically every person gave a positive reaction.

It is not amiss, at this point, to trespass just beyond the border of the area which we have discussed, to mention the tuberculosis situation in Oklahoma Indians, because that state alone has practically as many as Arizona, New Mexico and California combined, or nearly 30 per cent of the total in the country. The death rate from tuberculosis among them in 1937–1939 was 154.0 per 100,000. This is appreciably better than in the other states we have discussed, but is far above the average for the country and is four times the rate among white persons in the state.

TUBERCULOSIS MORTALITY IN ORIENTAL RACE STOCKS IN CALIFORNIA

This review would be incomplete without some reference to the nearly 200,000 persons of Oriental origin in California. The Japanese, comprising nearly three-fifths of the total, had a death rate from tuberculosis in 1937–1939 of 83.8 per 100,000. This is lower than in the other groups, but nearly double that of the white population, exclusive of the Mexicans. The death rate among the Chinese was very high, 179.8 per 100,000 in the same period. Filipinos, numbering nearly 40,000, had, next to the Indians, the highest mortality from the disease. They constitute the great bulk of the residual "other races" which had a death rate of 223.6 per 100,000 in 1937–1939.

In San Francisco, tuberculosis among the Chinese is a problem of major concern.[3] In a study (7), made a few years ago, both the reported case rate and the death rate from tuberculosis was three times as high as among white persons, but this ratio is probably too low, for there was evidence that the reporting of cases was relatively poor among the Chinese.

COMMENT

This review of tuberculosis mortality statistics in the Southwest, admittedly inadequate, at least gives a general picture of the extent of the problem in this area. The cases of tuberculosis among these race stocks in the Southwest constitute a sizable fraction of the total residuum of this disease in our country. If a measure of control were gained among them, it would be a real contribution to the final eradication of tuberculosis in this country.

What remains to be said about this problem is obviously not original; but it will bear repetition because not until these facts are more generally

[3] Since this paper was prepared, there has appeared a report by W. C. Voorsanger and G. B. Miller on an excellent study of tuberculosis among the Chinese in San Francisco (Am. Rev. Tuberc., 1941, *44*, 463).

appreciated by those who have the power to bring the necessary resources to bear, will measures vigorous and comprehensive enough be instituted. First and foremost let me say that the problem of tuberculosis among these peoples is not particularly different from that among white persons generally. Although the possibility of an inherent racial susceptibility to tuberculosis among these peoples has been suggested and, in part, explored, as the cause of their high mortality from tuberculosis, the weight of clinical evidence is against the validity of this conception. A much simpler explanation for the terrible findings that prevail here lies in the combined influence of low economic status, bad housing and domestic overcrowding, poor and insufficient diets, lack of elementary hygienic knowledge, insufficient medical care and the totally inadequate facilities for the discovery and treatment of tuberculosis. In this area, more especially in Texas and California, the problem of migrant farm laborers is most acute. Conditions are at their worst among them and their families. It seems to me very poor grace, in the light of these obvious facts, to pull in by the legs abstruse and unproved assumptions about the unfavorable genetic constitution of Negroes, Mexicans and Indians to explain away the bad health conditions that persist among them.

On the other hand, it would be grossly unfair to give the impression that the conditions among these people and in these states have been entirely neglected. Some progress has been made and, except perhaps among the Mexicans, death rates from tuberculosis among these racial groups are on the down trend. The problem has not been an easy one to solve and will remain so for very definite reasons. The wide open spaces, the differences of language and of social customs and differences in mode of life and outlook on life have not been conducive to the development of the types of organizations to fight tuberculosis, so effective in most of the country. Indeed, to win the coöperation of these peoples, we must modify our program somewhat, and in doing so seek whatever help can be obtained from the intellectual leaders among these races in formulating suitable modifications. In many places, alert public health officials are attempting to correct these shortcomings. The National Tuberculosis Association has done excellent work in organizing its national committees on tuberculosis among Negroes and among the Spanish-speaking peoples. These committees deserve the assistance and support of all who have responsibility for the health of these races. In California especially, much effort is being expended on the discovery and treatment of tuber-

culosis among the Mexicans. The Indian Service is doing much that is commendable for the diagnosis and care of tuberculosis and not the least is the very rapid increase in the number of hospital beds, now about 1,500, available for the care of the tuberculous of the race (8).

But in most other places, the problem is receiving insufficient attention and the facilities for the discovery and treatment of the disease are most inadequate. Let me be specific. The current report of the Texas Department of Health (9) notes that 75 per cent of the deaths from tuberculosis in the state occur at home; only 8 per cent in tuberculosis sanatoria. According to this report, there are in Texas 3,241 beds for the treatment of tuberculosis. This is less than one for every death from the disease. State and local authorities have provided only 2,500 beds, a fourth of which are in state hospitals for mental disease. For the colored, only two special sanatoria are provided with a capacity of but 194 beds. Sanatorium facilities for Mexicans in the border counties are negligible. Easily 3,000 more beds for tuberculosis patients are urgently needed in Texas.

In New Mexico, the situation is worse. While the total of approximately 1,000 beds (10) looks like a good number when compared with the annual number of deaths from the disease, most of these beds, outside of those provided by the Indian Service, are private and were established primarily for the treatment of nonresidents. There is only one state hospital, with a capacity of 86 beds. Arizona also seems to have abundant provision for the treatment of tuberculosis but again a very high proportion of these bed facilities is for nonresidents. Only 234 out of 1,623 beds (11) are in state and county sanatoria. The great majority of the beds in the state are in Federal hospitals under the supervision of the Veterans Bureau or the Indian Service.

The answer to the urgent problem of tuberculosis in the Southwest is not far to seek. What has been done to a remarkably successful degree in at least half the states of the Union can be done here. The job may be a little harder because of the inherent difficulties in the situation but these can be surmounted in due time. But basic to everything is a concerted and well planned effort, not a series of desultory and well intentioned trials which lead nowhere. As in every other community, the first step is provision for the discovery of cases which means the appointment of a sufficient number of well trained physicians and nurses and the installation of various facilities to make their work effective. But the finding of cases will be futile unless modern treatment away from home is at once

provided for cases as they are discovered. Running all through this problem is the fundamental necessity for a well conceived campaign of health education, preferably in the native languages, carried on through the schools, through the churches, through all types of organizations which reach the people.

It is clear that a program of this intensive type cannot be financed wholly by the local people. The very ones who need it most are least able to pay for it. It has become an established principle that in this type of situation, especially in such states as Arizona and New Mexico, a large share of the financial burden must fall on the Federal Government. The states, to be sure, should help to their full capacity and private philanthropy can likewise contribute support.

Steps of this type will bring results. But they will not solve the problem. To do that the steady stream of new cases must be blocked at its source through a radical improvement in the way of life of these people. For they are not enjoying an American standard and their bad tuberculosis record simply reflects their unfavorable environmental conditions. No permanent solution will be achieved until their low economic status is raised. It should not be necessary at this late date to make comments such as these because they are all too obvious. No one gains when a large fraction of the community lives in a manner which breeds disease. Bad conditions in one group of the population are a constant menace to the rest. Whatever will be spent to bring about a correction of these conditions will be the best investment the communities of the Southwest have ever made. The spiritual gains, in healthier and happier communities, will be real and great. But beyond that, the economic returns should be of such magnitude as to suggest unbridled usury.

If there were no other motive for correcting the conditions to which I have referred, self-interest would demand it. For, the native white populations of these states are certainly as favorably situated, economically and otherwise, as those in the Middlewest, yet the death rate from tuberculosis among them is far above that in other areas. This can only mean that the close and increasing contact between the disease-ridden minority races and the native whites maintains a high level of tuberculosis morbidity and mortality among the latter. Even the most careful and conscientious program for control of tuberculosis among this part of the white population, therefore, will lose, in effectiveness, unless simultaneous attack is made on all the important foci of infection in the area.

I am, essentially, an optimist. I sincerely believe it is in the cards

that this tuberculosis situation can be beaten. Is it too much to hope that this very meeting in San Antonio, so delightful in many ways, may release the needed determination and effort to bring the desired solution? It would be a fine thing if in the annals of our Association we would remember this meeting as the occasion when definite steps were launched for an intensive and final attack on tuberculosis among the under-privileged races of the great Southwest.

SUMMARY

1. The mortality from tuberculosis throughout the southwestern part of the United States is far above the average for the country. In this region are the two states with the highest rates in the country, namely, Arizona and New Mexico.

2. The high death rates from tuberculosis in this area are largely due to the high frequency of the disease among Negroes, Indians, Mexicans and Oriental race stocks. In much of the area, the death rates among non-Mexican whites are also above the average for the country.

3. The high mortality of tuberculosis among Mexicans and colored persons reflects their poor social and economic status, combined with their ignorance of fundamentals of personal hygiene and the wholly inadequate facilities for the diagnosis and treatment of tuberculosis among them.

4. To cope with the bad tuberculosis situation in the southwest, it is first necessary that diagnostic and curative facilities for tuberculosis be greatly expanded. Some states need financial aid from the Federal Government for this purpose.

5. Health education programs should also be set up, in the planning of which the cultural level and language differences of these peoples require consideration.

6. No permanent solution of the tuberculosis problem in the area may be expected until the economic condition of these peoples is improved.

SUMARIO

1. La mortalidad tuberculosa en toda la región sudoeste de los Estados Unidos es muy superior al promedio para el país en conjunto. En dicha región radican los dos Estados que tienen los coeficientes máximos del país, o sean Arizona y Nuevo México.

2. La elevada mortalidad tuberculosa en dicha zona débese en gran parte a la frecuencia del mal entre los negros, los indios, los mexicanos y

los descendientes de orientales. En gran parte de la zona, la mortalidad entre los blancos no mexicanos también es muy superior al promedio para el país.

3. La elevada mortalidad de la tuberculosis entre los mexicanos y personas de raza negra refleja su desfavorable estado social y económico, combinado esto con ignorancia de los elementos de la higiene personal y la falta de suficientes medios para el diagnóstico y tratamiento de la tuberculosis en ellos.

4. A fin de atender a esta desfavorable situación tuberculosa en el sudoeste de Estados Unidos, es necesario primero acrecentar considerablemente los medios de diagnóstico y de tratamiento, y para ello algunos Estados necesitan ayuda económica del Gobierno Federal.

5. También deben establecerse planes de educación sanitaria, los cuales deben tomar en cuenta el nivel cultural y el lenguaje de los distintos grupos.

6. No cabe esperar ninguna solución permanente del problema tuberculoso en la zona descrita hasta que haya mejorado el estado económico de la gente.

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SOLITARY FOCI OF TUBERCULOSIS[1,2]

Their Development and Progress—Assmann Foci, Caseous Nodular Tuberculosis and Tuberculomata

PHILIP H. PIERSON[3]

Solitary tuberculous lesions of the lung are of interest both because of the manner in which they develop and because of their potentialities. Some are doubtless quite benign but many break down, disseminate and lead to progressive or fatal disease. The lesions I wish to consider are not newly described but perhaps a review of this phase of tuberculosis has given me a clearer understanding and suggested more rational management of early lesions. Whether a given solitary lesion should be called an Assmann focus, a caseous nodular tuberculosis or a tuberculoma depends largely upon three factors: (*1*) stage of the disease, (*2*) size of the lesion and (*3*) its location; but the pathological process may be similar in each instance, in character if not intensity. Not a great deal has been written on this latter subject, which is quite surprising in view of the many solitary lesions which are seen.

DEFINITION

It might be well to define what is meant by a solitary lesion. It is one which is roughly spherical in shape, of fairly uniform density and with sharply defined borders, which set it off from other pulmonary structures. These masses may be less than 1 cm. in diameter or as much as 5 cm.

In 1916 Gerhartz described cases of isolated infraclavicular infiltrates but in 1921 Assmann more fully elaborated on this lesion as evidence of "the early infiltrate," a caseous, pneumonic form generally located in the infraclavicular region, rather than in the apex. It existed without physical signs, having the tendency to enlarge and disintegrate, although some receded as time went on. Such lesions were often associated with caseous pneumonic or multiple nodular

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forms of the disease. In 1925 he explained in more detail a soft, indefinite shadow located just below the clavicle generally in its outer portion and stated that in his experience it was seen in a group of medical students and assistants in the pathological and clinical institutes who were examined on the first suspicion of pulmonary disease. Subjective and objective findings were minimal or lacking. Roentgenological studies showed only the localized area which in serial studies changed from a hazy infiltrate to a sharply defined shadow of uniform density, which later liquefied in some instances with the formation of a cavity. In some cases there was no sputum but, if any was expectorated, it might show many tubercle bacilli. In more progressive cases small spots were seen around the isolated shadow, originating through lymphogenous dissemination from the focus.

In 1923 Wessler and Jaches described the same condition and referred to the areas as distinct, circumscribed shadows, varying in size from millet seed to 1 or 2 cm. in diameter and located in the outer infraclavicular region. Early lesions were indistinct due to the exudative character of the disease and, as the periphery absorbed, a dense central area became more sharply defined and homogeneous. They did not mention cavitation but said that several such areas might appear in the same region.

In 1926 Warnecke reported 19 cases of early infiltrates found in his sanatorium and the ages of these women varied from twenty-nine to forty-nine years. He concluded that neither age nor occupation played a part in the development of Assmann foci. They were probably not evidence of primary infection, for in only 4 was there any significant enlargement of the hilar lymph nodes and in every case a calcified primary focus could be found. Tubercle bacilli were present in 4 cases and cavity formation in 2.

In 1929 Redeker and Walter discussed the site of this early infiltrate as described by Assmann and found in 145 cases that 53 per cent were in the distal part of the infraclavicular region, 28 per cent in the midfield, 12 per cent in the lower field, 5 per cent in the subclavicular zone and 2 per cent in the apex. They felt that the fluoroscope was of more value in visualizing these areas than the X-ray film because, by rotating the patient, the lesion could be brought out from behind ribs and the scapula. They reported 5 cases that had been studied pathologically by other observers and a caseous focus with rather firm encapsulation was found. In the surrounding tissue small foci were seen at times. They quote Aschoff, Puhl and other German pathologists as favoring the view that this early infiltrate originated from exogenous reinfection. Loeschke found that in 90 per cent of adults evidences of apical tuberculosis were present and that a fine-grained spread in the apex was rarely serious while the coarse-grained spread, of which Assmann focus was an example, could lead to serious consequences.

Beitzke, in 1931, concluded that the early infiltrate was a caseous pneumonia, generally with a somewhat older centre, surrounded by a fresh hepatization;

in 1928 Stefko had reported 4 cases, examined pathologically, which showed productive nodules with caseation, surrounded by collateral inflammation described as gelatinous pneumonia.

Then followed papers by Fleischner, Herrnheiser, Jablokov, Alexander, Ulrici and Neumann, who felt very much as the previous authors—namely, that the early infiltrate, including the picture presented by Assmann, may occur anywhere in the lung, that it is a manifestation of reinfection disease, that it may absorb, remain stationary or progress. They suggested in regard to treatment: observation, gold, tuberculin or pneumothorax.

Straub, Brock and Schemmel described these round foci as existing in rather advanced disease and found that they were generally stationary in spite of the progression of the other lesions, although they did excavate rarely. Pathologically Straub describes these lesions as round, structureless, caseous, calcified masses surrounded by fibrous tissue which occasionally had undergone hyalinization.

In summary, these observers have found solitary, spherical foci existing either in the development of an early infiltration, which was most often found in the infraclavicular region, or in the presence of extensive disease located anywhere in the lung. They frequently remained stationary but might spread and pathologically they represented caseous pneumonic areas with hyalinization or calcification sometimes taking place.

TUBERCULOMA OF THE LUNG

A tuberculoma is a circumscribed mass of tuberculous granulation tissue without surrounding inflammation; there may be present small, scattered areas of caseation. It is reported at times as occurring in the brain, iris, ischiorectal region, gastro-intestinal tract and elsewhere. However, it is obvious that in the literature on phthisis the term tuberculoma in the lung has come to mean any tuberculous nodule or mass surrounded by a fibrocaseous or hyalinized wall. This term is very elastic and may include small, as well as large, circumscribed areas of tuberculous tissue, which usually caseate and hence form a cold abscess; the pathological process resulting from localized, encapsulated caseous pneumonia is very similar. There is very little in the literature about pulmonary tuberculomata and this may be due to the fact that in the lung, where motion is constantly taking place, large tuberculous abscesses tend to progress and rupture and rarely remain isolated. It is possible that in the future we may recognize this condition more frequently due to our knowledge of partially and completely blocked cavities. A partially blocked cavity leads to inflation but a completely blocked one may lead

to deflation—absorption of the air and encapsulation of the inspissated material. Where the oxygen supply is cut off from tubercle bacilli they may lose their virulence and in time may die.

Not all such circumscribed masses in the lung are tuberculous even when evident tuberculosis is present. The same differential diagnosis is to be considered whether these masses are large or small and must include pyogenic abscess and bronchiectatic pockets, encapsulated interlobar empyema, neoplasms, such as primary or metastatic carcinoma, sarcoma and rarer benign or malignant tumors, infarcts and localized pneumonia, ecchinococcus cysts, congenital or acquired cysts and rarely syphilis.

Graham and Singer in 1936 reported 3 cases of calcified pulmonary abscesses simulating tumors in individuals thirty-nine, thirty-three and thirty years old, respectively. The lobes containing these tumors were removed and no definite pathological or bacteriological evidence of tuberculosis was found. One patient had been treated previously for tuberculosis and the mass, 3 cm. in diameter, consisted of a laminated, calcified wall with central necrosis. In their second patient the mass was 3.5 x 2.5 x 2 cm. and represented an old, partly healed, interlobar empyema or a healed, inspissated abscess. Around the periphery of this mass there was a zone of round cells, infiltration, granulation tissue and atelectatic lung. Their third case showed a mass 2 x 5 cm. in diameter, its central portion containing what appeared to be pus. Microscopically it was not pus. This cavity, lined with ciliated epithelium, was surrounded by a thin plate of bone. It may have been originally a cyst or a healed interlobar empyema with a bronchial communication.

Churchill removed at operation a tuberculoma 6.5 x 4.5 cm. in diameter, the wall of which was 1 cm. in thickness. The periphery of the mass was smooth with an overlying thickened pleura. A smaller, rounded shadow in the upper lobe of this patient had disappeared.

Haight and Farris in 1939 reported the accidental finding of a mass 6 cm. in diameter in the base of a right lung which upon removal showed an area of active tuberculosis next to the mass, although smears and cultures from the mass were negative for tubercle bacilli. The wall consisted of concentric laminations. It was their conclusion that "a circumscribed tuberculous lesion undergoing slow peripheral extension and concurrent calcification of centrally contained necrotic tissue would conceivably produce a tuberculoma similar to the one described here."

CASE REPORTS

The cases that I have chosen to present may be roughly divided into five groups: (*1*) Assmann foci, (*2*) caseous pneumonic nodules, (*3*) com-

pletely blocked cavities and large tuberculous abscesses, (*4*) tuberculomata and (*5*) other lesions (primary carcinoma of the lung and caseous coccidioidal nodule) simulating the solitary masses previously described.

(*1*) *Assmann foci:* In each of the 3 cases there is a solitary infraclavicular focus, representing the only visible tuberculous area in the lungs.

Case 1: M. G. The lesion was picked up on routine X-ray examination and was symptomless (figure 1). At first there was a hazy pneumonic patch which within a year showed absorption of the exudate (figure 2) leaving one area about 2 cm. in diameter and another about 1 cm. in diameter, sharply circumscribed and of uniform density (figure 3). This picture fits quite accurately the description of Assmann and I think would show a caseous nodule surrounded by a fibrocaseous wall. Pneumothorax was instituted for one and one-half years and the focus has remained about stationary or become a little smaller (figure 4). If the encapsulating wall has become firm enough, this lesion may remain inactive indefinitely.

The other 2 cases, case 2, F., (figures 5 to 9), and case 3, C. G., began as either a small caseous nodule (figure 5) or a ring (figure 10) (empty cavity), progressed (figures 11 and 12) and broke down (figure 13) disseminating the infection to the surrounding tissue. I think this spread was by continuity (figure 14). One patient, C. G., was controlled by pneumothorax and the other healed gradually by rest alone.

Figures 15, 16 and 17 represent cases 4 to 6 in this group. These 3 cases are representative of a large series, some of which broke down and showed a cavity in a relatively short time. I think it is wiser to consider such areas as evidence of active tuberculosis and institute pneumothorax at an early date. A relatively short period of treatment will probably protect the patient against an early spread and shorten the length of time that would otherwise be necessary for him to rest. Pneumothorax is a relatively safe procedure and with it the patient can continue his work.

(*2*) *Caseous nodular foci:* The 2 cases, case 7, McM., (figures 18 to 21), and case 8, H. C., represent quite a group of cases that present themselves either in the exudative or the nodular stage. The end result—a caseous focus—may be easily overlooked because it is small and may lie behind a rib (figure 23); nevertheless, it is of potential danger. H. C. came to autopsy and the nodule in his right lung suggested a bronchiectatic pocket filled with caseous material (figure 22). One section through this nodule showed a bronchus whose wall was infiltrated with nontuberculous tissue

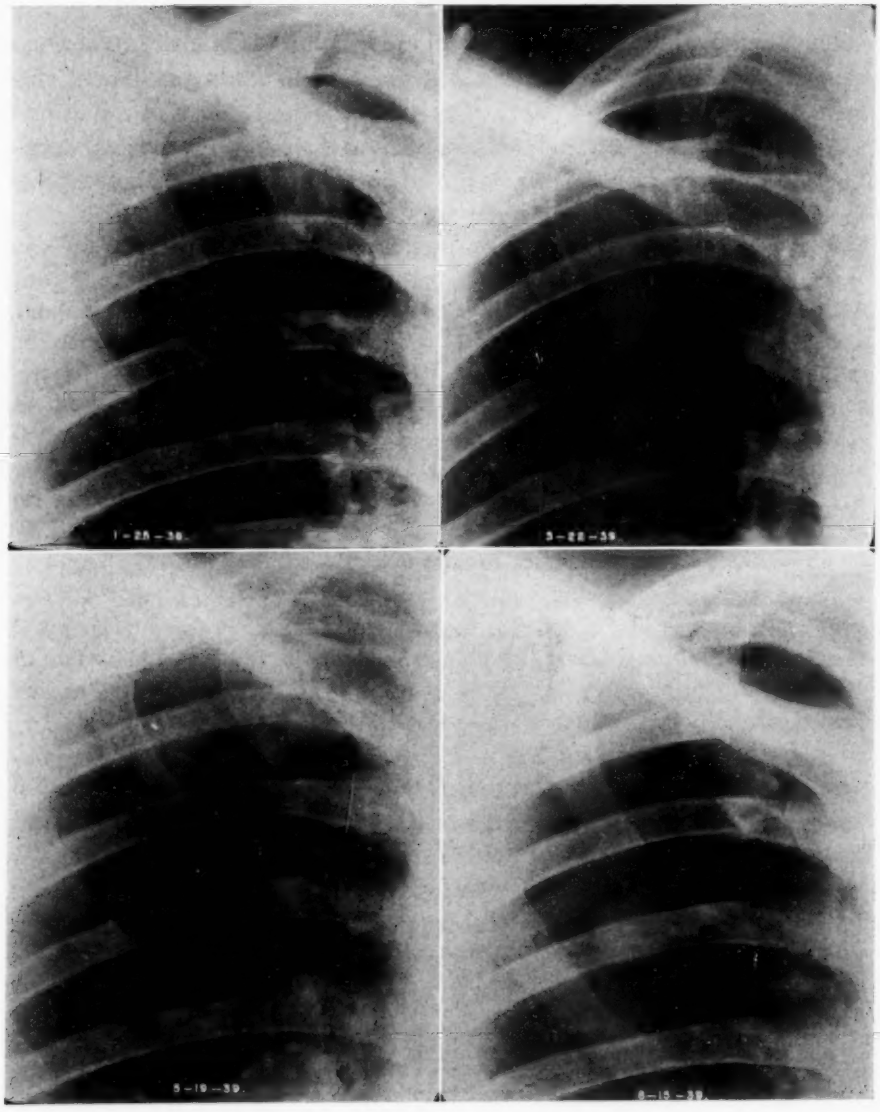


FIG. 1 (upper left). Case 1. Assmann focus, early stage, first interspace.
FIG. 2 (upper right). Case 1. Considerable exudation absorbed.
FIG. 3 (lower left). Case 1. Uniformly dense nodule.
FIG. 4 (lower right). Case 1. Treated with artificial pneumothorax.

and this may have been a factor which caused the accumulation of debris (figures 24, 26, 27, 28). In the other lung was a denser nodule behind a rib (figure 25) and this, on section (figure 29), showed a caseous mass

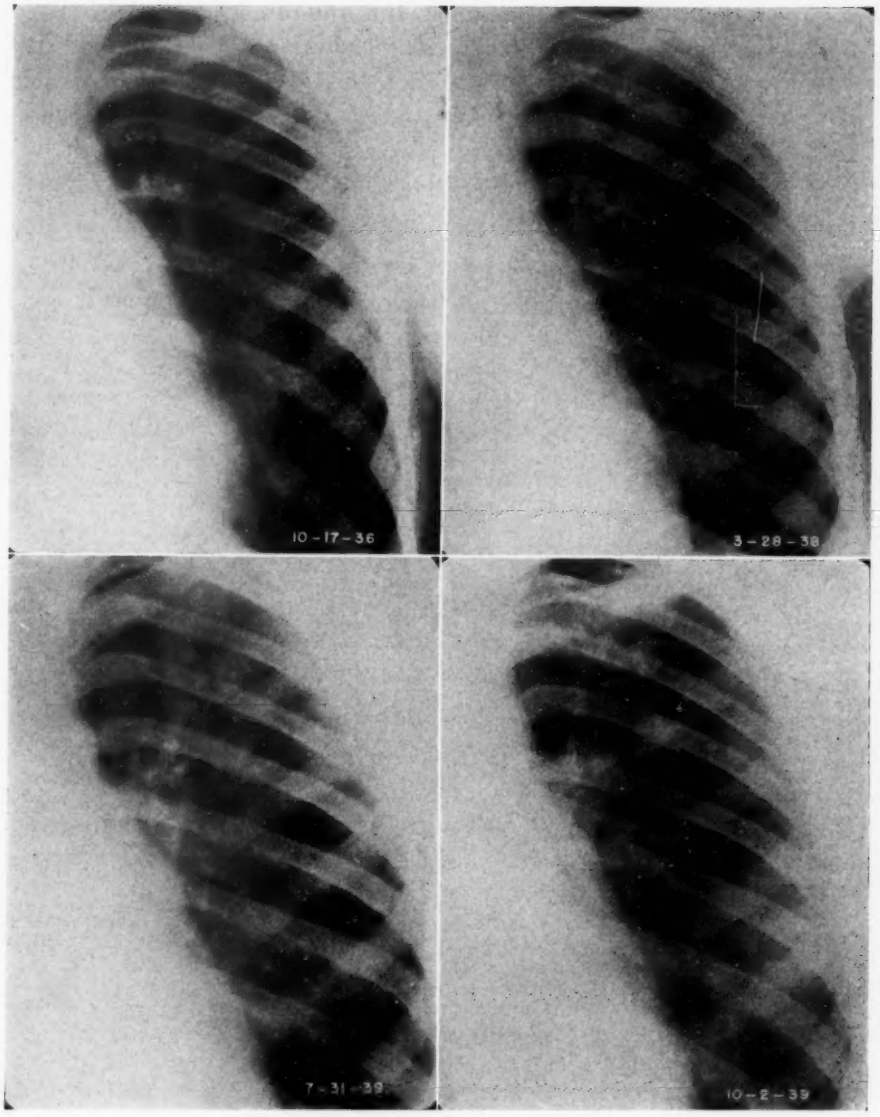


FIG. 5 (upper left). Case 2. Assmann focus, small, left first interspace.
FIG. 6 (upper right). Case 2. Seventeen months later, lesion larger.
FIG. 7 (lower left). Case 2. Focus has broken down and disseminated.
FIG. 8 (lower right). Case 2. Recession of the lesion under rest care alone.

surrounded by a fibrous wall in which no giant cells or tubercles were found. I have sectioned several such nodules and have found the same condition present—a fibrocaseous wall about a caseous centre. In one

of these I found recently tubercle bacilli in the caseous material. They represent, then, a focus of tuberculosis which may break down and disseminate locally. In the case of N.S. reported later, this is just what happened. Cases 9, 10 and 11 (figures 30 to 32) belong in the same group.

(*3*) *Completely blocked cavities*, forming either small or large tuberculous abscesses offer an intriguing subject for study. In recent years we have heard much about partially blocked cavities with their tendency to form

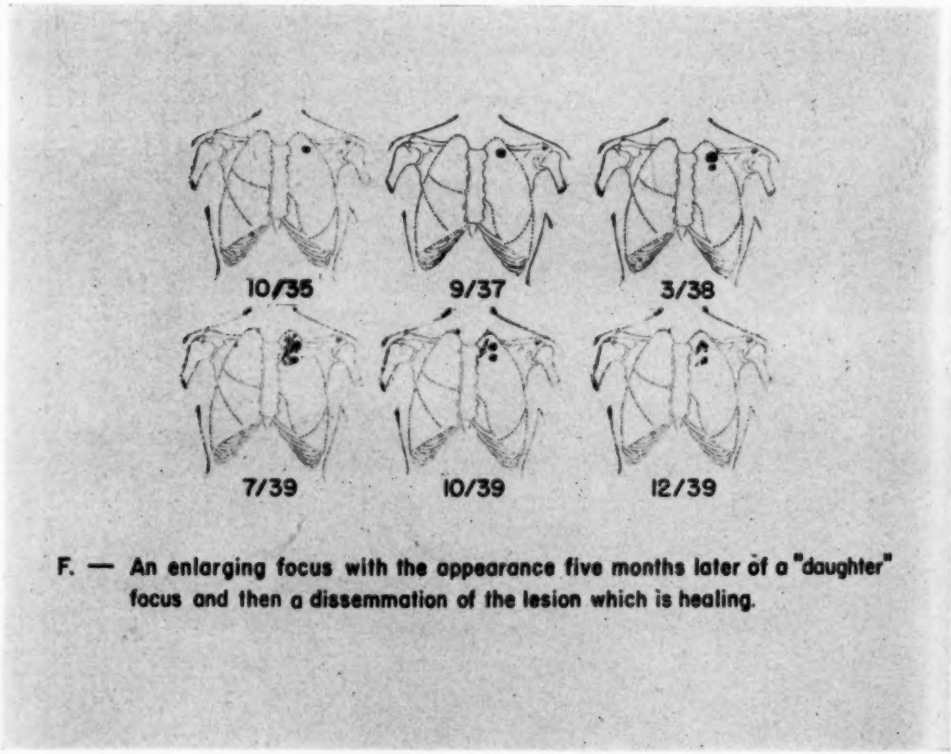

10/35
9/37
3/38
7/39
10/39
12/39
F. — An enlarging focus with the appearance five months later of a "daughter" focus and then a dissemmation of the lesion which is healing.

FIG. 9. Diagrammatic presentation of case 2.

tension cavities, and about Coryllos' theory that cavities heal when a complete occlusion of the bronchus occurs.

In case 12, J. R., we have two areas of interest, a small spherical area above and a larger cavity with a fluid level below (figure 33). The latter becomes completely filled with caseous material and the fluid level disappears (figure 34), while the upper one opens and balloons up to several times its previous size. Lipiodol injected directly into this cavity in 1936 (figure 35) is still there

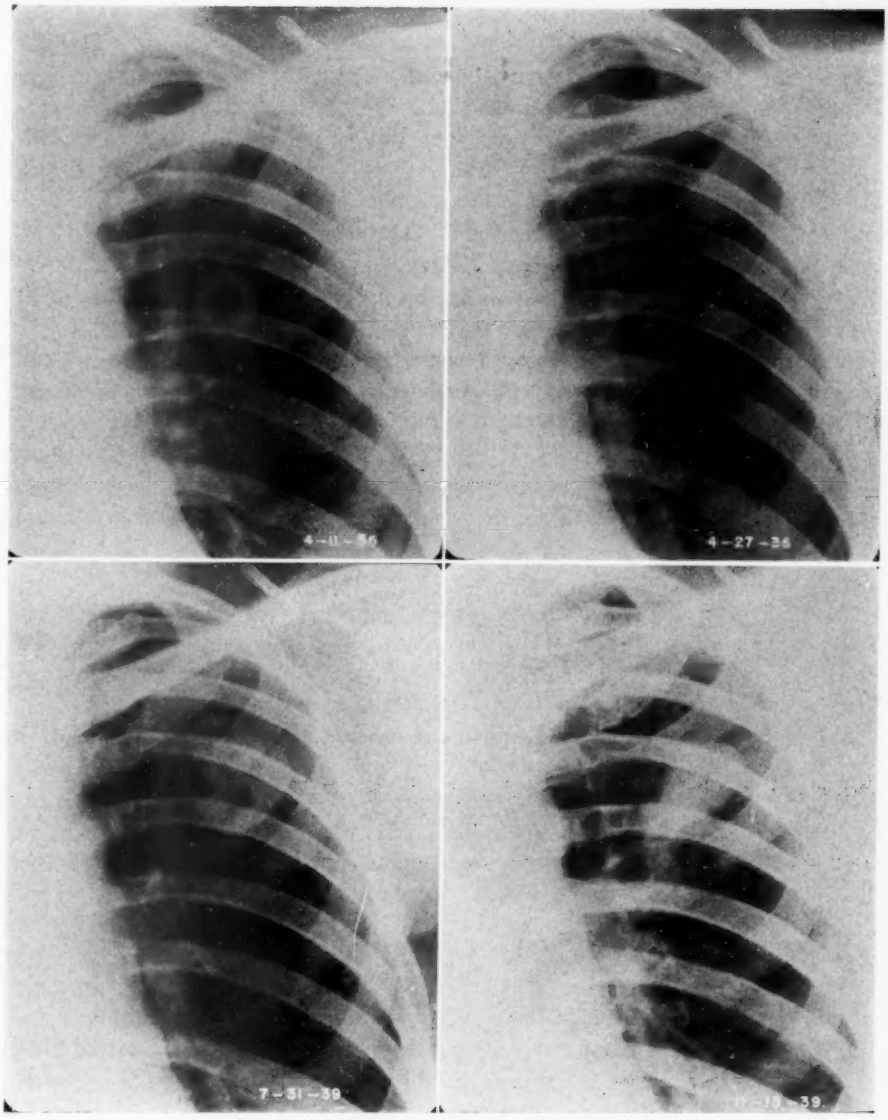
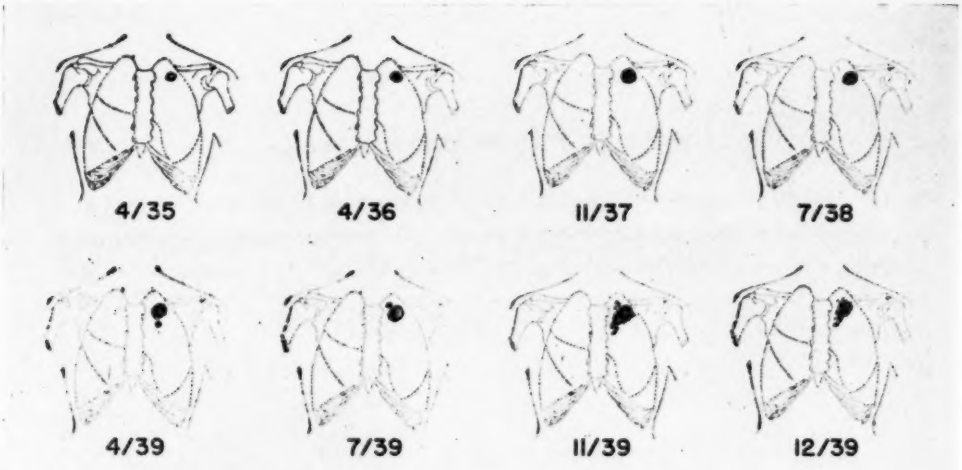


FIG. 10 (upper left). Case 3. Excavated Assmann focus under second rib.

FIG. 11 (upper right). Case 3. One year later, filled with caseous material, and larger.

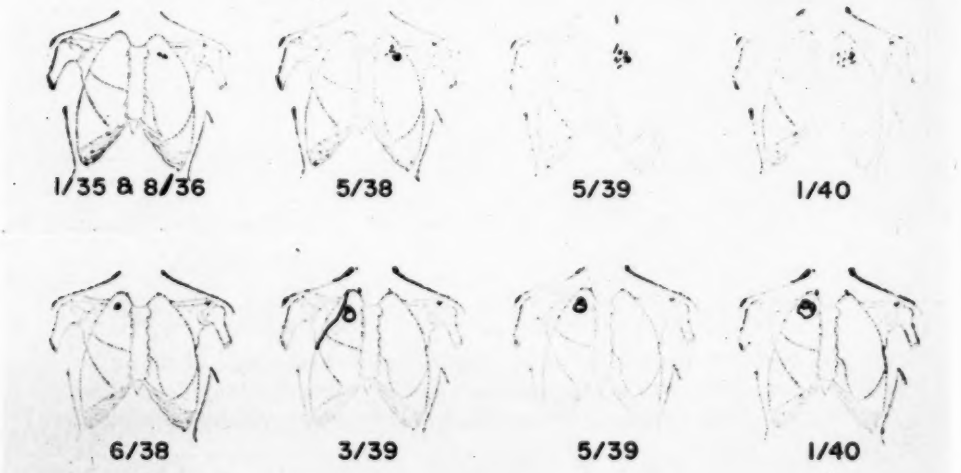
FIG. 12 (lower left). Case 3. Three years later, larger and containing vacuoles. A "daughter" cyst above it.

FIG. 13 (lower right). Case 3. Four months later, dissemination of the lesion, successfully treated with artificial pneumothorax.



C. G. — An annular shadow was first seen in April 1935 became an Assman focus one year later, then increased in size, and from July 1938 to July 1939 vacuoles appeared as well as "daughter" foci. In November 1939 there was a spread of the lesion and pneumothorax was instituted. This represents an active lesion of 4 1/2 years.

E. P. — Six months after this focus was discovered its center became rarified.



A. B. — This Assman focus in the right apex remained stationary in spite of the developement of a tension cavity in the same region, treated by pneumothorax unsuccessfully. Eight months after the pneumothorax was abandoned the original cavity had become larger and the center of the focus had liquified.

Figs. 14–17 (For legend see page 85.)

in 1939 after thoracoplasty (figure 36). It would seem then that the upper opaque shadow originally represented a nodule without ulceration into the bronchi. Later a communication with a bronchus formed but in this there was a partial stenosis and the cavity became inflated. Again the bronchus became completely closed and has remained in this condition. The same inference may be applied to the lower cavity, that is, it became a nodule after occlusion of its bronchi (figure 37).

In case 13, T. S. E., the same is true—a uniformly opaque, sharply circumscribed area (figure 39) has replaced a cavity with a fluid level (figure 38) —another instance of an isolated mass being the encapsulation of caseous material in a completely blocked cavity.

As illustration of somewhat larger masses there are case 14, M. M., and case 15, N. S. M. M. is a nurse whose solitary lesion was first discovered in February, 1940 (figure 40) because she had a respiratory infection which persisted for three or four weeks. This infection cleared up shortly and no tubercle bacilli were found in her sputum. The check-up in October, 1940 was done at the request of her doctor and the films eight months apart show quite a considerable increase in the size of the mass (figures 41 and 42). Dr. Emile Holman aspirated some thick, caseous material, in which tubercle bacilli were found. I instituted a pneumothorax to see whether this would delay the rather rapid increase in the size of this abscess. It has apparently accomplished this from the report I received, but I think probably a lobectomy will be advisable. If this mass ruptures, bacilli may be spread throughout her lungs.

Case 15, N. S. was first seen in 1927, and the lesion in his left lung (he has dextrocardia) was thought to be quiescent (figures 43 and 44). He entered the University of California in January, 1939 and the lesion had increased markedly and appeared very dense, possibly with a calcified wall (figures 45 and 46). At that time he had a slight cough. By September he had malaise, fever, fatigue and was expectorating a large amount of greenish sputum, which was found to be positive for tubercle bacilli (figure 47).

It is possible that this mass gave very much the same appearance as did those reported by Graham and Singer, and Haight and Farris. In the first report it was impossible to identify the aetiology of the tumors, but Haight described the mass he removed as consisting of a wall made up of concentric laminations, encapsulating necrotic tissue. The smears and

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FIG. 14 (upper). Diagrammatic presentation of case 3.

FIG. 15 (upper middle). Case 4. Assmann focus.

FIG. 16 (lower middle). Case 5. Age ten. Healed tuberculosis left apex with calcifications; stationary until May, 1938, when an Assmann focus appeared, broke down in 1939 and is absorbing in 1940.

FIG. 17 (lower) Case 6. Assmann focus.

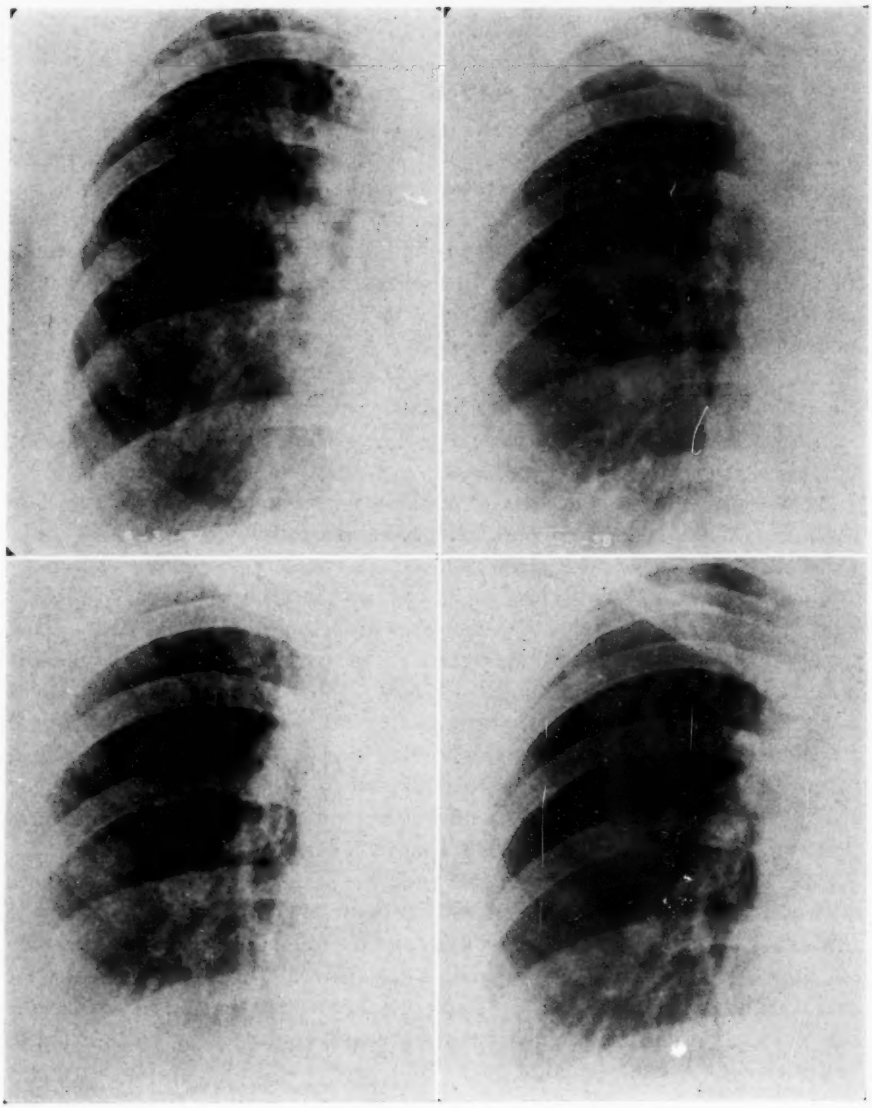


FIG. 18 (upper left). Case 7. Extensive exudative lesion, right lung.

FIG. 19 (upper right). Case 7. Seven months later, absorption of much of the exudate. Two definite nodules beginning to appear in lower half.

FIG. 20 (lower left). Case 7. Sharper definition of same two caseous nodules.

FIG. 21 (lower right). Case 7. Caseous areas present, but smaller.

(Legends for figures on facing page)

FIG. 22 (left upper). Case 8. Circumscribed discrete nodule in center of right lung.

FIG. 23 (left upper middle). Case 8. Caseous nodule, outer portion left lung, under third rib.

FIG. 24 (right upper middle). Case 8. Gross specimen, caseous nodule, right lung.

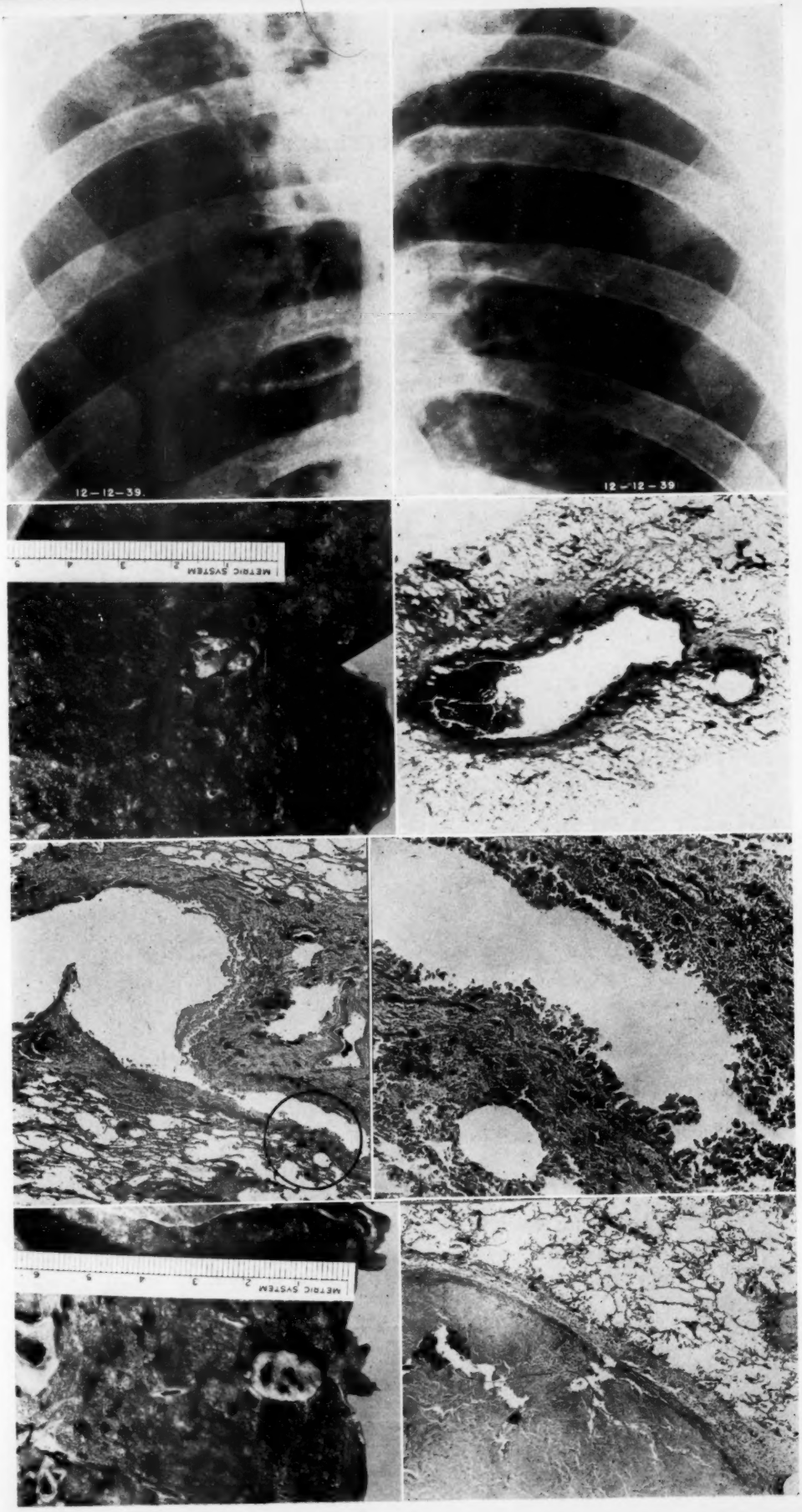
FIG. 25 (left lower middle). Case 8. Gross specimen. Caseous nodule, left lung.

FIG. 26 (right lower middle). Case 8. Low power microphotograph of nontuberculous bronchiectatic pocket, right lung.

FIG. 27 (right upper). Case 8. Higher magnification showing the bronchus leading to this.

FIG. 28 (left lower). Case 8. Higher magnification showing bronchial epithelium.

FIG. 29 (right lower). Case 8. Microphotograph showing fibrocaseous nodule, left lung.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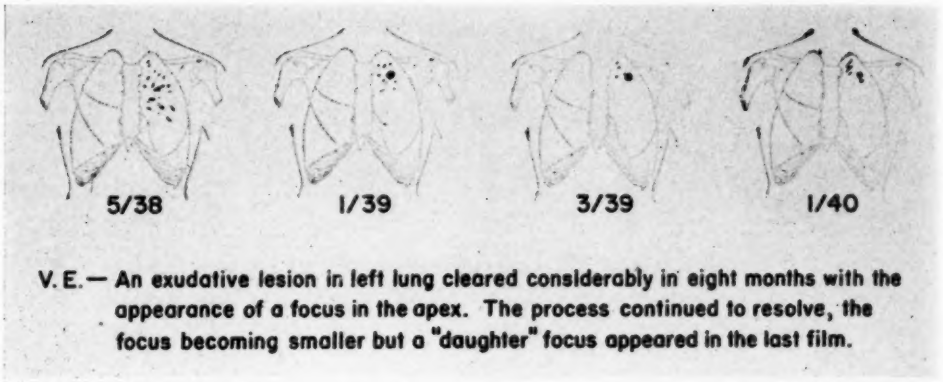
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3/39
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V. E.— An exudative lesion in left lung cleared considerably in eight months with the appearance of a focus in the apex. The process continued to resolve, the focus becoming smaller but a "daughter" focus appeared in the last film.
4/39
6/39
9/39
1/40
M. D — Two months after this focus was discovered its center rarified and within three months it was uniformly dense again and had almost disappeared 4 months later.
7/38
12/38
2/39
6/39
A. C.— A solitary focus in the right lower lung field is changing in size at each of these periods.

FIG. 30 (top). Case 9. Caseous nodular lesion.
FIG. 31 (middle). Case 10.
FIG. 32 (lower). Case 11.

cultures showed no tubercle bacilli. It is a question whether this should have been called an abscess or a tuberculoma in the pathological sense. I mention this because perhaps clinically the term tuberculoma of the

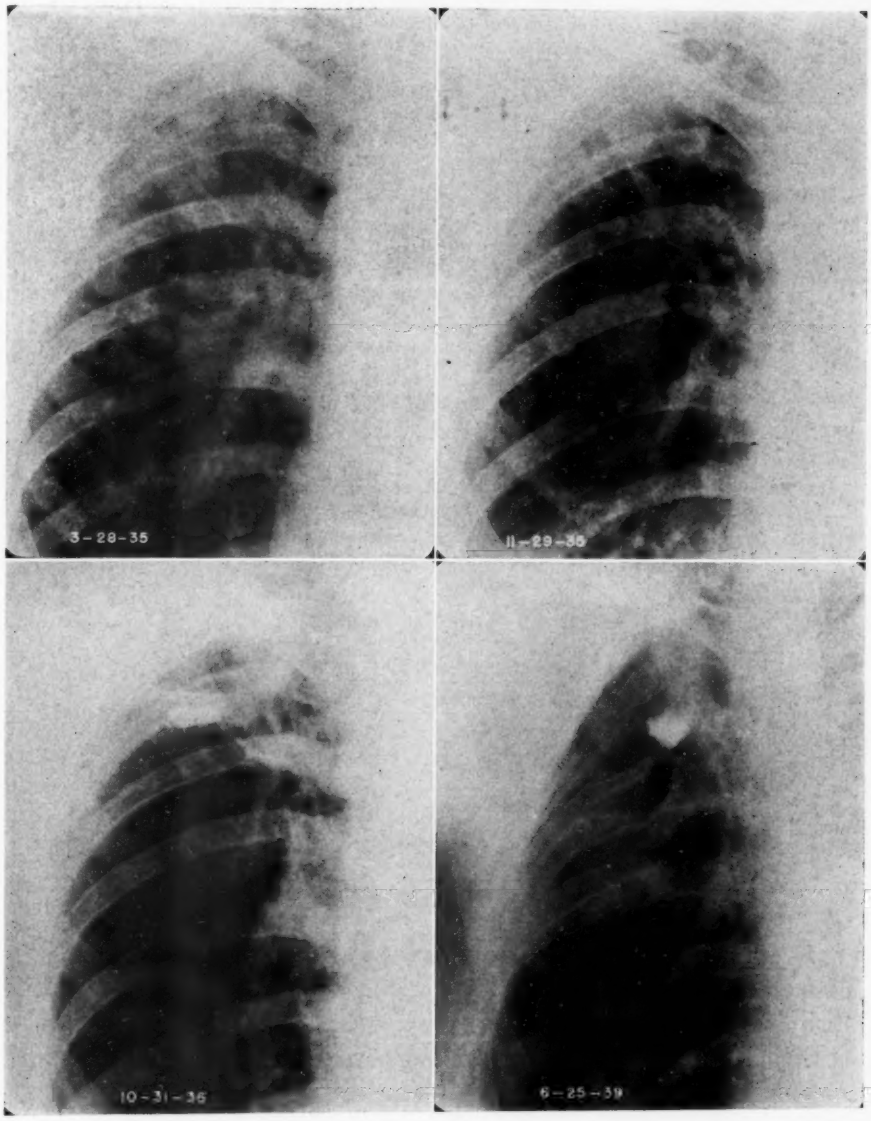

FIG. 33 (upper left). Case 12. Caseous nodule first interspace. Cavity in second interspace.

FIG. 34 (upper right). Case 12. Caseous nodule remains stationary. Cavity has completely filled in.

FIG. 35 (lower left). Case 12. Upper caseous nodule becomes tension cavity containing injected lipiodol. Lower caseous nodule stationary.

FIG. 36 (lower right). Case 12. Lipiodol persisting in upper completely blocked cavity for about three years. Lower caseous nodule not visible due to thoracoplasty.

lung and a fairly good sized tuberculous abscess are synonymous in the literature.

(*4*) *Tuberculoma:* Dr. Paul W. Gebauer of Cleveland was good enough to send me the record of case 16, E. D., (figure 48), a patient who had been followed for two years. He had had a cough and haemoptysis. The tumor was too hard to biopsy at thoracoscopy but was "shelled out" at operation and proved to be a tuberculoma (figure 49). A serosanguineous fluid developed, which on the 19th day showed Type 29 Pneumococcus but no tubercle bacilli. This was drained and the lung completely re-expanded.

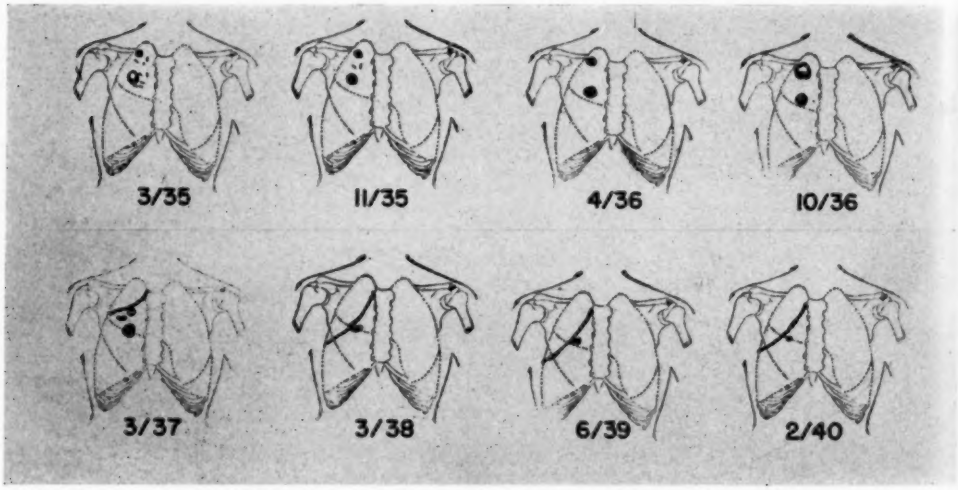

FIG. 37. Diagrammatic presentation of case 12.

(*5*) *Nontuberculous solitary masses:* Case 17, H. K., (figure 50), male, a patient of Dr. Leo Eloesser, was seen at the San Francisco City and County Hospital with an apical tuberculosis and the mass at his left base as shown in the X-ray film. This mass was needled and the first time

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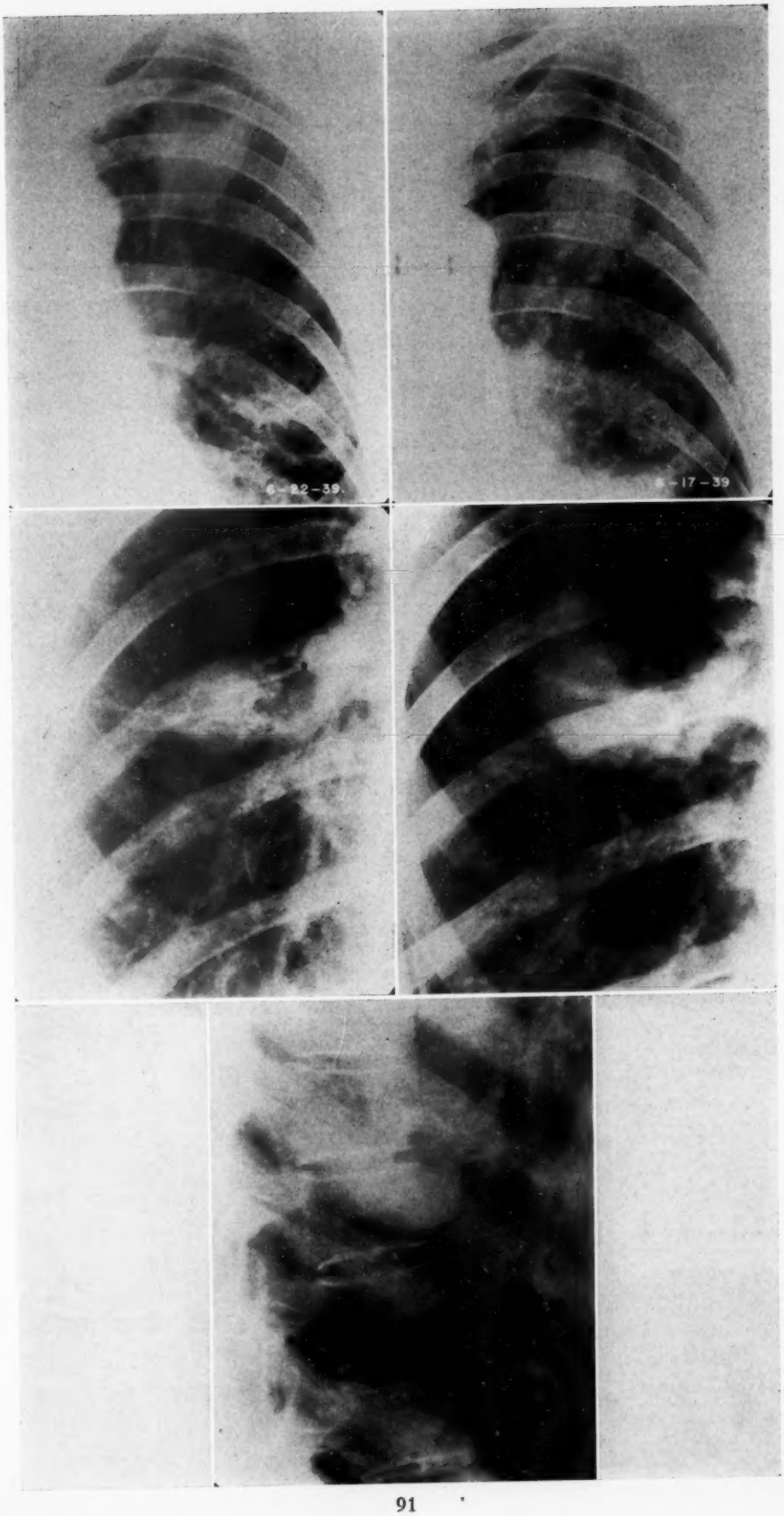
FIG. 38 (upper left). Case 13. Cavity left upper with fluid level. Tension cavity at base.

FIG. 39 (upper right). Case 13. Upper cavity completely blocked off is full of caseous material after institution of artificial pneumothorax. Basal cavity has disappeared.

FIG. 40 (middle left). Case 14. Tuberculous abscess as seen on February 10, 1940.

FIG. 41 (middle right). Case 14. Tuberculous abscess as seen October 9, 1940.

FIG. 42 (lower). Case 14. Abscess confirmed by needle puncture. Artificial pneumothorax instituted and has controlled development. Lobectomy is probably indicated.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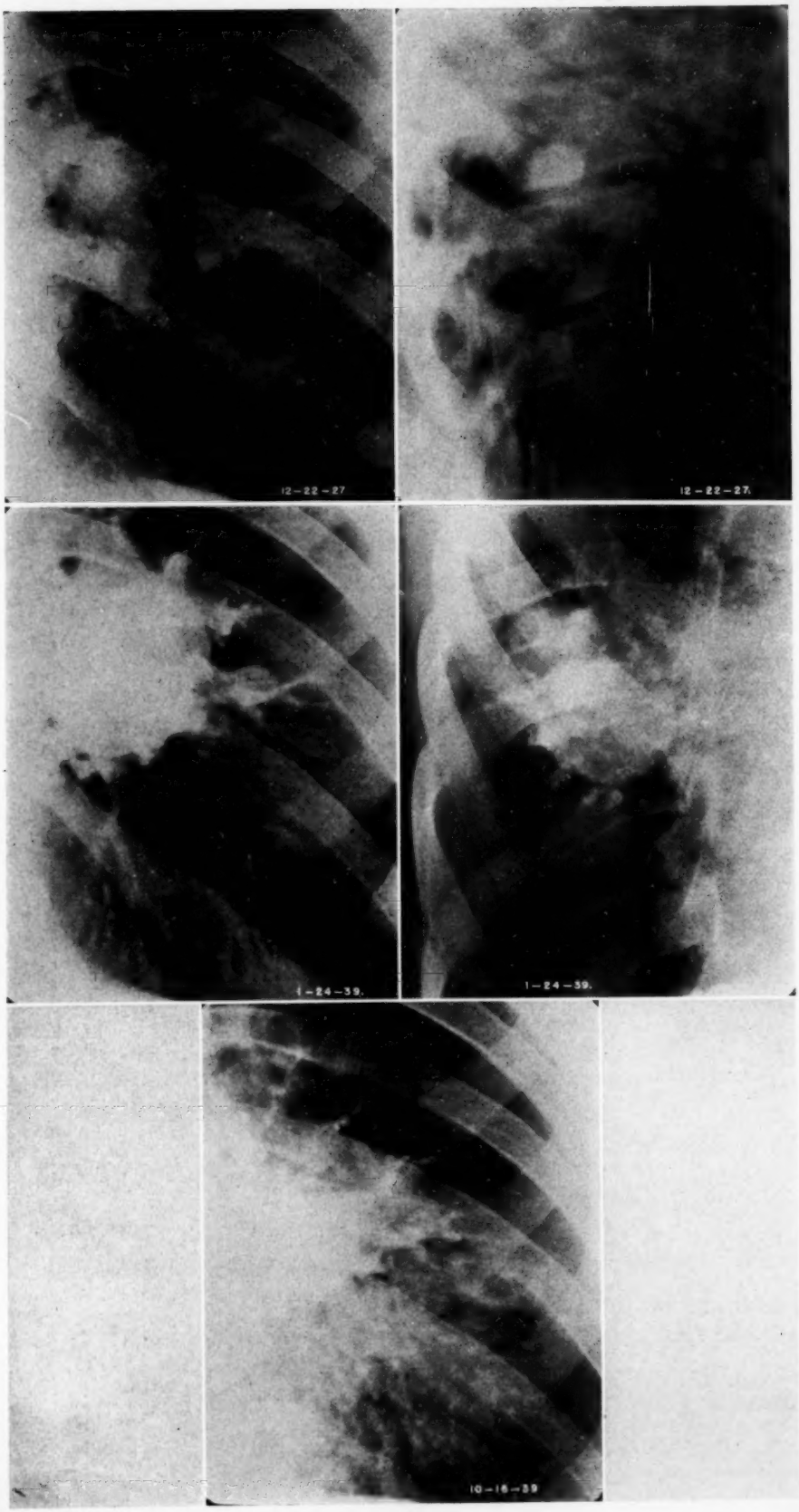
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only some debris was obtained in which there were no malignant cells nor tubercle bacilli. On the second attempt a few tubercle bacilli were found, so a catheter was inserted and suction applied. The size of the mass increased and the drainage had no effect except that some of the necrotic centre was removed. A biopsy was done which showed carcinoma. The mass was removed and it proved to be composed entirely of primary bronchogenic carcinoma. The tubercle bacilli obtained had doubtless entered through an open bronchial communication from the apical lesion to this mass.

The films of case 18, L. C., were loaned to me by Dr. Victor Schulze of San Angelo, Texas. This patient had an acute coccidioides (figure 51) and within four months the exudation had subsided to such a degree that a spherical mass was evident (figure 52). Whether this will go on to form a calcification similar to a Ghon's tubercle, time alone will tell. In a man of fifty-three the diagnoses considered were primary coccidioides, pneumonia with the development of an abscess, malignancy (primary bronchogenic carcinoma) and a possible tuberculosis. It is interesting to compare this caseous pneumonic focus, a primary complex, with the similar shadows seen in the reinfection disease complex described by Assman.

It is my intention to make serial sections through some of these tuberculous masses in order that a more definite conclusion may be reached as to whether some represent a cavity with a completely blocked bronchus.

SUMMARY

Solitary tuberculous foci of several types have been described. They have been grouped according to the stage of the disease and their size, location and development. They all present very much the same pathological picture—a caseous centre surrounded by a fibrocaseous or calcified wall. It is possible that a completely blocked bronchus may be the cause of some of these abscesses. The differential diagnosis has been discussed.

It has been shown that many of these solitary nodules break down and disseminate bacilli. After a short period of rest and observation a

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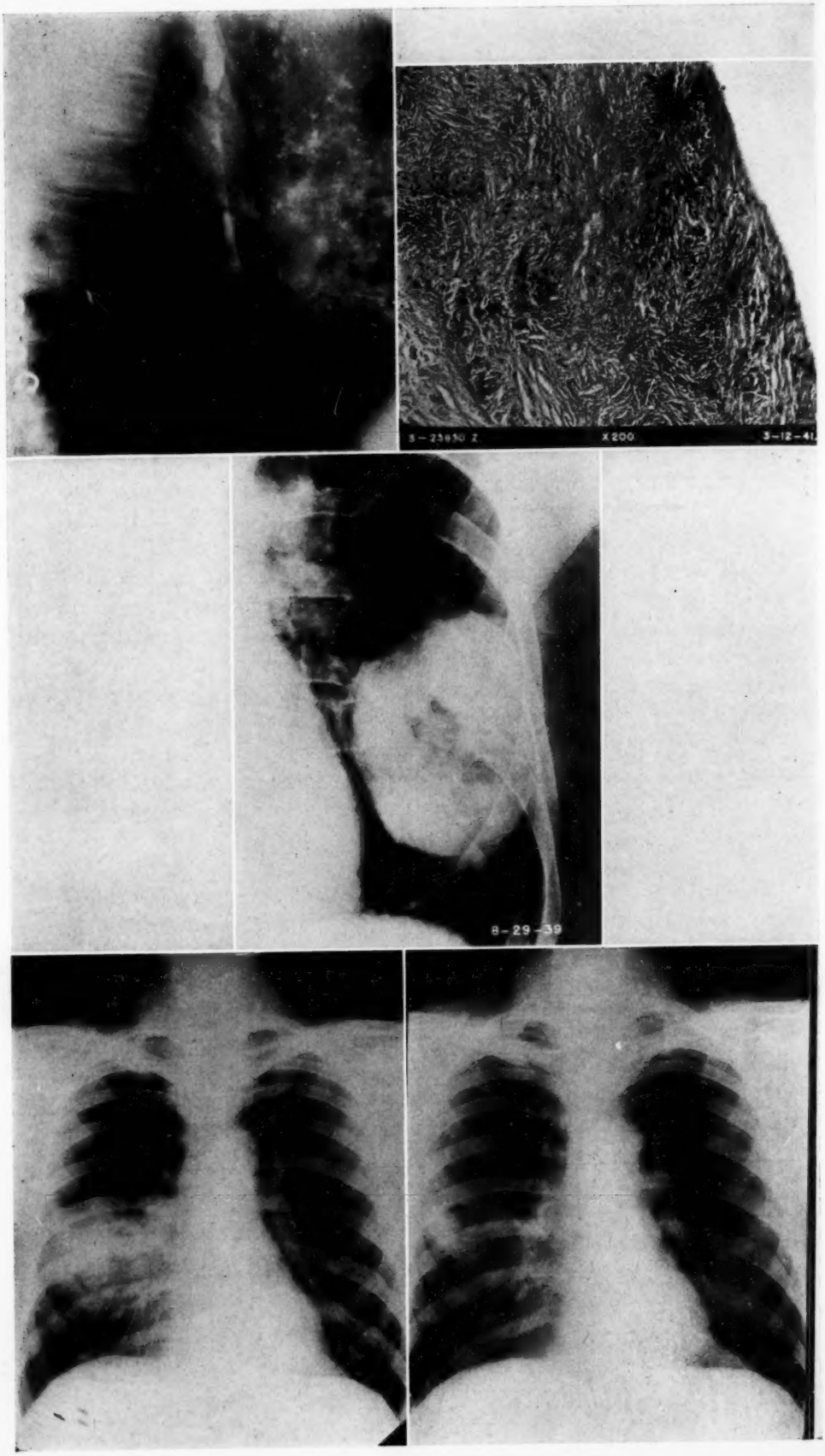
FIGS. 43 and 44 (upper). Case 15. Tuberculous abscess lower lobe.

FIGS. 45 and 46 (middle). Case 15. Appearance of same twelve years later showing enlargement and partial calcification of wall.

FIG. 47 (lower). Case 15. Dissemination of above lesion nine months later.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pneumothorax may be of help in walling off the process and keeping it localized. If the mass is large and the only visible evidence of tuberculosis, lobectomy may be indicated. This procedure with its risk may be preferable to dissemination, which is often difficult to control.

SUMARIO

Descríbense en este trabajo focos tuberculosos solitarios de varios tipos, clasificándose conforme a la etapa de la enfermedad y su tamaño, situación y desarrollo. Todos ellos presentan un cuadro patológico muy semejante: un centro caseoso rodeado de una pared fibrocaseosa o calcificada. Es posible que un bronquio completamente obstruído pueda ser la causa de algunos de estos abscesos. Discútese también el diagnóstico diferencial.

Se ha demostrado que muchos de esos nódulos solitarios se desintegran y diseminan bacilos. Después de un breve período de descanso y observación, un neumotórax puede ser útil para emparedar el proceso y mantenerlo localizado. Si la tumoración es grande y constituye el único signo visible de tuberculosis, puede estar indicada la lobectomía. Esta operación, aun con el riesgo que la acompaña, puede ser preferible a la diseminación que resulta a menudo difícil de cohibir.

I want to express my appreciation for the opportunity of presenting cases to the following: San Francisco Department of Public Health, the University of California Medical School Tuberculosis Service, San Mateo Community Hospital, Dr. Paul Gebauer and Dr. Victor Schulze.

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FIGS. 48 and 49 (upper). Case 16. Tuberculoma, removed at operation (courtesy Dr. Paul W. Gebauer).

FIG. 50 (middle). Case 17. Primary bronchogenic carcinoma. Tubercle bacilli entered this from the apical lesion, confusing the diagnosis for a time.

FIG. 51 (lower left). Case 18. July 9, 1940. Primary coccidioides (courtesy Dr. Victor Schulze).

FIG. 52 (lower right). Case 18. November 14, 1940. Four months later, resolving, simulating an Assmann focus.

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CLINICAL NOTES

SIMULTANEOUS BILATERAL SPONTANEOUS PNEUMOTHORAX[1]

L. R. GAETÁN

The occurrence of simultaneous bilateral pneumothorax is considered a rarity in the medical literature. According to Glickman and Schlomovitz (1) who reported a case in 1936 and made a review of the literature, there were only 82 authenticated cases reported up to that time. Among the proved cases, ruling out those of traumatic origin, the order of frequency according to aetiological factor was as follows: tuberculosis, emphysema, pneumonoconiosis, bronchopneumonia, asthma, congenital cysts, tumors and interstitial fibrosis.

In a search of the literature we find that there have been reported another 10 cases since 1936. Seemingly the cases reported have increased. This is probably due to the interest displayed in trying to discover cases early and to improved diagnostic procedures.

CASE REPORT

P. J. H. C., a forty-three year old, white, married male, school teacher, was admitted to the Sanatorium on April 23, 1940, with a history of cough, expectoration, haemoptysis, fever, night sweats, anorexia and loss of weight of eight months' duration.

Physical examination on entrance revealed a poorly developed and poorly nourished individual weighing 89 pounds. Except for signs of extensive bilateral pulmonary disease there were no other pathological findings.

An X-ray film of the chest taken on April 26, 1940 (figure 1) revealed bilateral tuberculosis of a fibrocaseous type with ulcerations in the left lung. His sputum was positive for Koch's bacillus; Wassermann and Kahn tests were positive.

The patient was running a temperature of 37° to 37.4°C.; expectoration was 50 g. a day. Due to the extensive lesions no collapse therapy was indicated. Patient was put on complete bed-rest. On June 6, 1940, about six weeks after admission, the patient had a sudden attack of dyspnoea while sitting in bed rubbing his arms with alcohol. Dyspnoea increased and patient became cyanotic; pulse was thready and very rapid. Examination of the chest revealed a tympanitic note on percussion in both hemithoraces. On auscultation breath sounds were diminished. The diagnosis stood between bilateral sponta-

[1] From the Insular Antituberculosis Sanatorium, Rio Piedras, Puerto Rico.

neous pneumothorax and cardiac insufficiency with pulmonary emphysema. The patient was given intranasal oxygen and morphine $\frac{1}{4}$ grain. Immediate improvement was noticed, cyanosis disappeared but patient remained slightly dyspnoeic. The next morning an X-ray film was taken (figure 2) and it revealed a bilateral pneumothorax. The manometric pressures on the left side were $-4, +10$. Five hundred cc. of air were removed, leaving pressures of $-12, 0$. In the right side the pressures were $-6, 0$. No air was removed, patient was comfortable. There was no elevation of temperature, no pleural effusion.

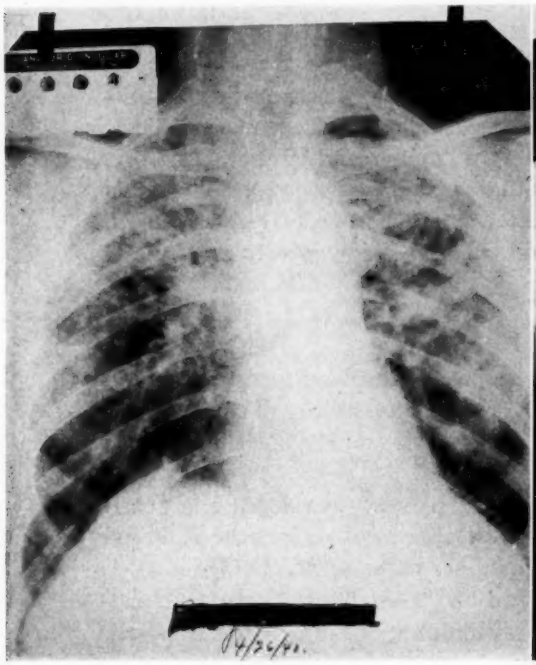

FIG. 1

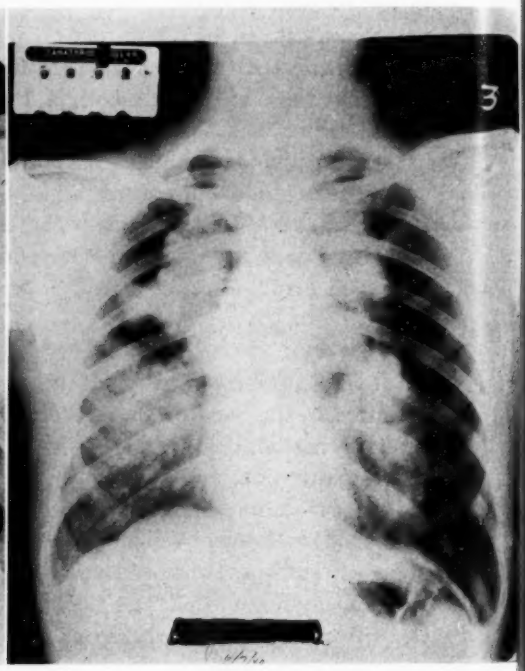

FIG. 2

In view of the fact that the patient could tolerate bilateral collapse in spite of the extensive lesions, pneumothorax was maintained on both sides. The patient improved in his general condition, temperature was normal and expectoration was reduced to 10 g. daily. On August 2, 1940, almost two months after the first episode, the patient had a second attack of sudden dyspnoea. Manometric pressures in the left pleural cavity were $-1, +6$, where the last manometric pressures had been $-8, -3$. At this time 900 cc. of air were removed leaving pressures of $0, +4$. The patient at this time was extremely ill, necessitating repeated punctures and finally had to be put on constant deflation. The temperature rose to 38.5°C. and remained at that level for

two weeks when it began gradually to become normal. X-ray film of the chest at the time revealed slight reëxpansion on the right side but persistent pneumothorax on the left side with beginning pleural effusion. Patient was fully recovered six weeks after the second accident. Pneumothorax was discontinued and patient is still alive and has improved on strict bed-rest. Last X-ray film of the chest, taken on December 13, 1940, reveals both lungs completely reëxpanded with persistence of lesions in the upper two-thirds and marked emphysema of both bases.

DISCUSSION

This is a case of simultaneous spontaneous pneumothorax, with recurrence of the spontaneous pneumothorax on the left side. The radiological image and repeated sputum examinations have confirmed the presence of extensive bilateral pulmonary tuberculosis. It is a known fact that an accident of this sort is generally fatal in patients with extensive lung involvement. In this instance the patient has survived two such accidents. The absence of temperature reaction in the first episode and the relatively small pleural reaction in the second one, makes one think of the possibility of the coexistence of emphysematous blebs in both lungs together with tuberculous lesions. One would be very much inclined to consider the areas that caused spontaneous pneumothorax as bullous emphysema rather than a tuberculous necrosis, judging from the clinical picture.

SUMMARY

1. A case of simultaneous spontaneous pneumothorax with recurrence on one side is reported.
2. In spite of the extensive bilateral tuberculous involvement the aetiological factor is not clear.
3. The patient is alive one year after the initial accident.
4. Ten more cases have appeared in the literature since 1936.

SUMARIO

1. Preséntase un caso de neumotórax incipiente simultáneo con recurrencia unilateral.
2. A pesar de la extensa invasión tuberculosa bilatera, no se ha esclarecido el factor etiológico.
3. El enfermo está vivo al año del accidente inicial.
4. Desde 1936 han aparecido 10 casos semejantes en la literatura.

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SPONTANEOUS PNEUMOPERICARDIUM

In a Case of Apparently Arrested Pulmonary Tuberculosis

HAROLD GUYON TRIMBLE,[1] J. LLOYD EATON AND KENNETH THOMPSON

During the course of collapse therapy of pulmonary tuberculosis with artificial pneumothorax or pneumoperitoneum, the occurrence of emphysema in the mediastinum or the tissues of the chest, neck and face is unusual but not rare. It is even more uncommon when this condition is found when no pneumothorax is being given. It seems to be very rare indeed, especially in the absence of trauma, for a spontaneous pneumopericardium to develop. Under that title there have been two cases reported in the recent French literature (1, 2), both with associated spontaneous pneumothorax. One additional case (3) was found. The following is submitted as an example of spontaneous pneumopericardium as the sole complication, which developed in a patient who, in the past, had had alternating bilateral pneumothorax collapse and in whom the tuberculosis was apparently arrested and both lungs reëxpanded (right lung reëxpanded for five and one-half years and left for two years).

CASE REPORT

A twenty-three year old male was admitted to the Lung Service, Fairmont Hospital of Alameda County, August 6, 1932 with a diagnosis of pulmonary tuberculosis. An acute parenchymal lesion with a three and one-half cm. cavity was present in the right upper lobe. Sputum was positive. Right pneumothorax was induced. Collapse appeared adequate by January, 1933 and his course was uneventful. A right phrenic evulsion was performed in April, 1935. The lung was allowed to expand (a small amount of pleural fluid developed) and expansion was complete in July, 1935 after adequate collapse for thirty months.

On November 16, 1935, a soft infiltration was found in left subclavicular region and a cavity was present one week later. The lesion was controlled by artificial pneumothorax that was expanded voluntarily after adequate collapse of thirty-six months (January, 1939).

Follow-up examinations showed no change in his pulmonary lesions by fluoroscopy. He continued well, maintained his weight and was entirely without symptoms. Last examination was on November 26, 1940.

On January 22, 1941, five and one-half years after the right and two years

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after the left lung had reëxpanded, while driving to work in the afternoon (on night shift) he noticed a peculiar dull aching beneath the lower sternum. He had had no respiratory infection, no unusual exercise and had previously awakened from a normal sleep. He noticed the aching off and on while at work, but at no time did it become severe. When he returned home from work at 2:00 a.m. on January 23, he noticed a gurgling sensation in this same area associated with each heart-beat. He took his temperature and found no fever. He slept fairly well, but by the next morning the discomfort and the gurgling seemed more pronounced and the temperature by mouth was 100°F. A physi-

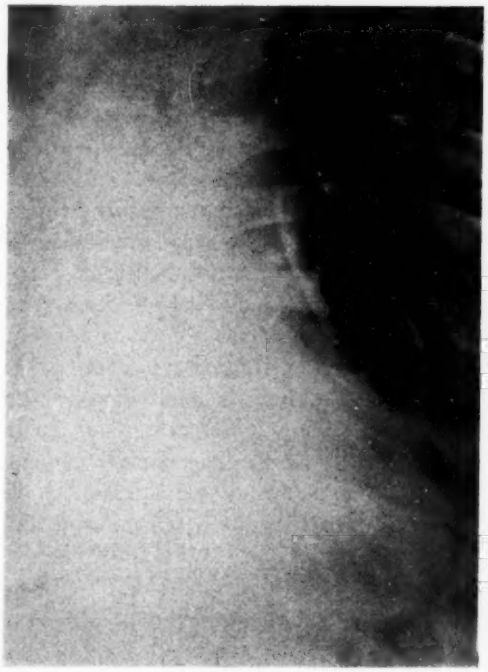

FIG. 1

cian was called (K.T.) who noted a peculiar water-like sound following each systole. The patient was hospitalized.

On entry to the hospital his temperature was found to be 100.6°F., which was the highest elevation; after twenty-four hours he was afebrile. The blood count was essentially normal with the exception of slight leucocytosis. Fluoroscopy and X-ray examinations were done on the day of entry and revealed a small amount of air distending the pericardial sac and completely surrounding the heart. A small amount of fluid was also seen, which agitated violently with each systole. X-ray films, including spot films, were taken from various angles and confirmed the diagnosis of hydro-pneumopericardium (figure 1).

There was no air or fluid in the pleural cavities of either side, and no air demonstrable in the mediastinum or subcutaneous tissues. There was no noticeable change in the pulmonary lesions. Gastric contents on January 28, 1941 were negative by concentration test for acid-fast bacilli. A guinea pig was inoculated but died two days later of intercurrent infection. The procedure was not repeated. By January 28 no air could be seen by fluoroscopy and the heart appeared of normal size. Physical examination and frequent fluoroscopic examinations have been negative since that time (June 11, 1941).

The mechanism of this spontaneous pneumopericardium is obscure. The patient previously had both lungs collapsed by artificial pneumothorax without any escape of air from the pleural cavities, which argues against any congenital abnormality of the pleural sacs. There apparently was no unusual physical exertion or trauma involved to account for any direct tearing which might allow the escape of air. The question as to the possible rupture of an emphysematous bleb, which so often is responsible for a spontaneous pneumothorax, must be considered, but the path of the air into the pericardial sac is not clear. On the other hand, it must be remembered that this patient did at one time have an active bilateral pulmonary tuberculosis and that some pleural effusion, which may or may not have contained tubercle bacilli, developed at the time of reëxpansion of each lung. It therefore seems likely that a tubercle involving the pleura and the pericardial sac broke through and allowed air to enter the pericardial sac. No signs of chronic pericarditis have appeared to date. It cannot be foretold at this time that a gradual thickening of the sac may not still occur.

As the mechanism of this spontaneous pneumopericardium is not clear, and as a tuberculous aetiology of the complication seems likely, it has been felt that, for the safety of the patient, he should be treated as a case of active tuberculosis.

SUMMARY

A patient is reported who developed a pneumopericardium about two years following cessation of pneumothorax treatment.

SUMARIO

Descríbese el caso de un enfermo que manifestó neumopericardio unos dos anos después de suspenderse el neumotórax terapéutico.

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AMERICAN TRUDEAU SOCIETY

Report of the Committee on Standard Laboratory Procedure

Minimum Laboratory Standards

Dr. Henry C. Sweany, Chairman
Dr. Emil Bogen — Dr. Arthur J. Vorwald
Dr. Max Pinner — Dr. H. S. Willis

The laboratory examinations recommended during the last generation for diagnosis, control of treatment and spread of tuberculosis are altogether too numerous to list for ready and practical use. The laboratories concerned vary with the size of the sanatoria and public health departments, and include laboratories located in different types of medical clinics and physicians' private offices. Obviously, no recommendations are possible that will be equally suitable or preferable for all.

There is a minimum, however, which is the least acceptable effort in searching for the tubercle bacillus. This minimum is represented in the following pages. Additional and more elaborate methods should be used whenever indicated and possible. As time goes on, this Committee will consider other methods, both old and new, and try to search out the simplest and most useful ones and make recommendations that are most practical and consistent with scientific progress.

I. Demonstration of Tubercle Bacilli

PREPARATION OF GLASSWARE

All glassware for handling sputum should be immersed in cleaning solution (50 grams of technical grade sodium dichromate are stirred into one liter of technical concentrated sulphuric acid, sp. gr. 1.82 +) for at least twenty-four hours, then carefully removed and thoroughly washed and dried, to insure the removal of any acid-fast matter that may adhere from previous use.

DEMONSTRATION OF TUBERCLE BACILLI IN SPUTUM

Collection of Specimen

A clean and sterilized, wide-mouthed bottle or container of 2 to 8 oz. capacity is recommended. The patient is instructed to deposit all sputum in

the bottle during the period prescribed. Where any long exposure to sunlight is liable to occur, brown glass is recommended.

The Direct Smear

Several lumps of mucopurulent sputum are lifted out on the end of a wooden tongue depressor or with a platinum loop and deposited in an open petri dish. For the sake of contrast the petri dish is placed on a black background. From this material the most purulent or caseous fleck in the specimen is picked out and smeared evenly over 3 to 4 square centimetres of the slide.

In examining large numbers of sputum specimens for tubercle bacilli, the autoclave method is most satisfactory and is the least time-consuming.

The specimens are brought to the laboratory in 2-oz. wide-mouthed bottles with snap-spring top, labeled with the patient's name. These are packed in paper sacks and autoclaved for fifteen minutes at 15 lbs. pressure. This procedure coagulates the purulent material in the sputum. The liquid in the specimen is then decanted into a waste jar and part of the coagulated material is smeared on slides with the aid of applicators or tooth picks. Sputum, which is mostly saliva, contains small specks of coagulated material, which are smeared and stained.

Concentration Method

If tubercle bacilli cannot be demonstrated in repeated direct smears, the sputum should be concentrated. If the expectoration is scant, sputum may be collected for from twenty-four to seventy-two hours or longer, if necessary to obtain a sufficient specimen.

Equal parts of sputum and 3 or 4 per cent aqueous solution of sodium hydroxide are well mixed and incubated at 37°C. with repeated shaking until the mixture is homogeneous, or the mixture of sputum and sodium hydroxide is shaken in a shaking machine, which requires, depending on the nature of the sputum, from fifteen to twenty minutes. (This procedure may advantageously be preceded by a twelve to fifteen hour incubation of the sputum specimen at 37°C.) The mixture is then centrifuged at high speed and the supernatant fluid is poured off to the last drop. Enough of normal hydrochloric acid is added to the sediment to make it neutral to a drop of phenol red solution. The indicator may be added before centrifuging. The sediment is spread thinly on a microscopical slide and stained.

As alternate methods, 3 vol. per cent hydrochloric acid (8 cc. of 37 per cent c.p., sp. gr. 1.18 diluted to 100 cc.) may be used instead of sodium hydroxide as a concentrating agent, although it does not concentrate as well.

Staining

The *Ziehl-Neelsen method* with low-heat staining is recommended. The technique is as follows:

1: Fix the specimen to the slide by means of gentle heat over a flame or electric stove.
2: Flood the slide with carbolfuchsin and heat for from four to ten minutes over a flame or an electric plate to steaming but not to boiling.
3: Rinse with water.
4: Decolorize with acid-alcohol until no more color is shown in the washings.
5: Wash in 95 per cent alcohol.
6: Counterstain with methylene blue for thirty seconds.
7: Wash in water.
8: Dry in the air over gentle heat.
9: Examine with oil immersion lens, taking care to wipe the lens well after each examination.

Carbolfuchsin solution:

10 cc. 3 per cent basic fuchsin (90 per cent dye content) in 95 per cent ethyl alcohol
100 cc. 5 per cent (by volume) aqueous solution of phenol

Acid-alcohol:

3 cc. hydrochloric acid, c.p., sp. gr. 1.18 (concentrated)
97 cc. 70 per cent ethyl alcohol

Methylene-blue solution:

3 cc. 1 per cent methylene blue (95 per cent dye content) in
95 per cent ethyl alcohol, diluted to 100 cc. with distilled water
Dilute 1:10 for use.

Because of its well established use, Loeffler's methylene blue may also be used. Preparation:

30 cc. 1 per cent methylene blue (90 per cent dye content) in 95 per cent ethyl alcohol
100 cc. 0.01 per cent aqueous solution of potassium hydroxide
This solution must be diluted with ten parts of water before use.

The *Cooper modification* of the Ziehl-Neelsen method is also recommended. The technique is as follows:

1: Make slide preparation as described above.
2: Flood slide with stain and gently steam for four minutes.
3: Cool until precipitate forms (approximately two minutes).
The precipitate must be allowed to form, for on it depends the success of the method.
4: Wash in water.
5: Decolorize for from five to ten minutes in acid-alcohol.
6: Wash in water.

7: Apply 95 per cent ethyl alcohol for two minutes.
8: Wash in water.
9: Apply brilliant green for ten to thirty seconds.
10: Wash in water and dry.

Carbolfuchsin (as above)	100 cc.
10 per cent aqueous solution of sodium chloride	3 cc.
95 per cent ethyl alcohol	95 cc.
Nitric acid—sp. gr. 1.42	5 cc.
95 per cent ethyl alcohol	
Brilliant green (90 per cent dye content)	1 g.
dissolved in	
1:10,000 aqueous solution of sodium hydroxide	100 cc.

After the sodium chloride is mixed with the carbolfuchsin, the completed stain must be kept warm. The stock bottle may be kept in the incubator, or the carbolfuchsin and the sodium chloride kept apart until ready to use, when they may be mixed in any desired quantity, but always in the proportions given above.

Culture Methods

If tubercle bacilli cannot be demonstrated by direct smear or after concentrating the sputum, isolation by cultural methods should be attempted. Since the sputum always contains fast-growing secondary microörganisms, it must be prepared for culture in such a way as to destroy such contaminants. This can be done by treating the sputum with alkali or acid. The sputum may be digested by concentration with 3 per cent sodium hydroxide, as described above; it may be digested with 6 per cent by weight sulphuric acid (c.p. sp. gr. 1.84, 3.4 per cent by volume), 3 per cent hydrochloric c.p. or 5 per cent oxalic acid. The neutralized sediment is then ready to be inoculated on culture media.

The seeding is done with a platinum loop or Pasteur pipette on culture tubes plugged with cotton and covered with rubber caps or in flat screw-top medicine bottles of 1 or 2 oz. capacity. The surface is covered thinly with the sediment, taking care not to pile it up in large lumps. The specimen should be labelled and placed in the incubator and examined after a few days to see if a contamination has occurred. The culture tubes should be examined every week for at least six weeks. Examinations should be made after three and six months before discarding.

Any suspicious colonies should be smeared and stained for acid-fast bacilli. If acid-fast bacilli are present, they should be inoculated into animals to test

for virulence; but in many instances when the colonies are entirely characteristic animal inoculation is not necessary.

Culture media: Preferably at least two of the following media should be used.

1: Loewenstein's medium, as modified by Jensen and Holmes; prepared as follows:

(*a*) Mineral salt solution:

Anhydrous potassium sulphate, 1.2 g.
Anhydrous magnesium sulphate, 0.12 g.
Magnesium citrate 0.3 g.
Asparagin, 1.8 g.
Glycerine, 6 cc.
Sterile water to make 300 cc.
Heat to dissolve; place in Arnold sterilizer for fifteen minutes; cool solution thoroughly.

(*b*) Starch solution: Put 15 g. potato flour in a sterile 1,500 cc. Erlenmeyer flask (pyrex) containing 100 g. sterile glass balls (approximately 4 mm. diameter). Mix glass balls and potato flour in dry state. *Slowly* add the minteral salt solution and mix thoroughly by a rotating horizontal motion. Then place *on* a boiling water bath, constantly agitating until a soft paste is produced. This usually requires about twenty or twenty-five minutes. Now place *in* a water bath at 56°C. for one hour.

(*c*) Egg fluid: Wash a dozen fresh hen's eggs with a brush in running water; drain; rinse each in alcohol and flame it. Break enough eggs into a sterile graduate cylinder to make 500 cc. (approximately 10 eggs); pour directly into the potato-flour-salt solution flask and mix thoroughly by shaking.

(*d*) Add 10 cc. of a 2 per cent aqueous solution of malachite green. (Note: This malachite green solution should be made previous to using and allowed to stand in incubator at 37.5°C. over night.) Mix thoroughly and filter through sterile gauze directly into a sterile separatory funnel. Tube and inspissate immediately at 85°C. for half an hour. Allow to remain in inspissator over night and inspissate next day at 75°C. for half an hour.

This batch of medium will make approximately 80 bottles (1 oz. size); 60 bottles (2 oz. size); or 100 culture tubes.[1]

2: Loewenstein's medium, as modified by Wooley and later by Petrik, is prepared as follows: Into a 3-quart pot are poured 500 cc. of whole eggs (about 10) and 100 cc. of egg-yolk, and the mixture is well beaten. To 500 cc. of a 12 volume per cent of glycerine in water are added 125 g. of thinly sliced, freshly peeled potatoes; this mixture is autoclaved at 15 pounds pressure for thirty minutes; after cooling, 400 cc. of the supernatant fluid are added to the egg

[1] Holmes, E. M.: J. State Med., 1934, *42*, 559.
Holmes, E. M.: Proc. Roy. Soc. Med., 1935, *28*, 43.

mixture and 12 cc. of a 2 per cent aqueous solution of malachite-green oxalate. The entire mixture is well beaten with an egg beater and filtered through several layers of gauze into a tubing funnel; 10 to 12 cc. are filled into each culture tube. The tubes, in proper position to give a long slant, are heated in an Arnold sterilizer or inspissator at 85°C. for one hour. The tubes are incubated for four days; contaminations are rare, if sterile technique is maintained throughout the procedure.

3: Petragnani's medium as modified by Saenz, is prepared as follows: In a 1,000 cc. Erlenmeyer flask containing 100 g. of glass balls, place:

250 g. fresh milk
16 g. potato flour
1.5 g. asparagin

Place on a boiling water bath for one hour; agitate frequently until the mixture has the consistence of puree. Cool to 60°C. and add 8 eggs and 2 yolks; agitate vigorously. Filter through sterile gauze and add:

24 g. glycerine
15 cc. 2 per cent aqueous solution of malachite green

Tube and inspissate at 85°C. for half an hour.

Animal Inoculation

The sputum is prepared in the same way for animal inoculation as for culture, but it must always be strictly neutralized. (For animal inoculation, digestion with sodium hydroxide is preferable to that with acids.) Sediment suspended in 2 to 3 cc. saline solution is injected into the groin of one or two guinea pigs. Subcutaneous injection is preferable to intraperitoneal injection because fewer animals will be lost prematurely and, in addition, it is possible to distinguish an inoculation from a spontaneous tuberculosis. In the rare but highly significant spontaneous infection, there is no enlargement or caseation of the inguinal lymph nodes. The inoculated animal should be killed as soon as the lymph nodes nearest the point of injection are easily palpable. If the lymph nodes do not become enlarged the animal should be killed six to eight weeks after the injection. Every inoculated animal must be autopsied. If inoculation yields a positive result enlarged and caseated lymph nodes are found near the point of inoculation, and the retroperitoneal, perigastric and hilar nodes are also enlarged and caseated. Tubercles are usually most abundant in the spleen, less common in the liver and lung and rare in the kidneys. The extent of the tuberculous involvement depends on the interval between injection and autopsy, on the number of bacilli in the inoculum and on their virulence. If the gross findings in inoculated guinea pigs are not entirely characteristic, smears and cultures for tubercle bacilli and histological sections must be prepared from the lesions.

DEMONSTRATION OF TUBERCLE BACILLI BY STOMACH LAVAGE

Certain patients are unable to raise sputum or their sputum is so scanty that bacilli are difficult to find. In either instance the bacilli may be swallowed and lie in the stomach which acts as a sort of catch basin. Washing out the stomach and examining the sediment will many times reveal tubercle bacilli that cannot be found in any other way.

The technique of stomach lavage is as follows: The examination is done on an empty stomach, preferably before breakfast. The patient drinks first about 6 oz. of water. A stomach tube, taken out of ice water, is then placed between the patient's teeth, and his head is brought forward by gentle pressure on the back of the head until the chin rests on the chest. The patient is asked to breathe through the mouth and, at the same time, to release the tube from between the teeth. At the moment of release the tube is inserted quickly but gently into the pharynx and on into the stomach three to four inches beyond the "mark." A compressed bulb is attached, and then released, after which two or three ounces of liquid will be obtained. This is centrifuged for forty-five minutes, the sediment smeared on slides and inoculated directly into guinea pigs. It is also treated and cultured in the same way as is described above for sputum, always verifying the pathogenicity of suspicious colonies.

DEMONSTRATION OF TUBERCLE BACILLI BY LARYNGEAL SMEARS

In patients who do not raise sputum, particularly in children, tubercle bacilli can sometimes be demonstrated in direct laryngeal smears. Material obtained from laryngeal swabs should be examined in smears, cultures and animal inoculations.

MICROSCOPIC EXAMINATION

The examination is done with an oil immersion lens after applying a drop of oil of cedarwood to the slide. The cedarwood oil should have a refractive index of 1.52. The illumination should be provided by a good tungsten lamp shielded by a blue glass, or the light should pass through a solution of 5 per cent copper sulphate in a florence flask. For continued work a binocular microscope is recommended. After each examination the lens should be thoroughly wiped with lens paper.

A minimum of five minutes' time, approximating 500 microscopical fields, must be spent before a slide may be called negative on routine examination.

Reporting Results

The results of the examination should be reported either *positive* or *negative* followed by the method used, such as direct smear, culture, etc. Any special features should be noted and written in, such as *atypical acid-fast bacilli, granules* or *suspicious microörganisms*, any of which will call for repeated examination and usually for cultures.

RULES FOR PROCEDURE IN VARYING CIRCUMSTANCES IN THE EXAMINATION FOR TUBERCLE BACILLI

For Diagnosis

1. Direct smear of a morning specimen and a specimen collected over a period of twenty-four hours, or as long a time as the circumstances require. (The direct smear may be omitted if the operator chooses to do a concentration.)
2. If the direct smear is negative, concentrate the same sputum specimen.
3. Culture the same specimens after concentration if the concentration is negative, if less than five bacilli are found in the smear, or if there is any possible doubt whether the acid-fast bacilli found are true tubercle bacilli.
4. If the first specimen is negative on microscopical examination, repeat the whole procedure on two subsequent occasions.
5. If sputum is not obtainable, gastric lavage should be performed and the sediment examined by direct smear, culture and animal inoculation.
6. A gastric lavage is recommended in patients having little sputum or if the specimens continue to be negative.

As a Gauge of Treatment

Patients with far advanced disease and positive sputum who are on routine rest treatment: direct smears every eight to twelve weeks, until they turn negative; then continue with concentration or culture at similar intervals.

Special treatment (pneumothorax, thoracoplasty, etc.) patients not far advanced but on bed-rest alone and patients on any change of treatment or in the early stages of treatment: Direct smear followed by concentration. If the direct smear is negative, it should be performed at monthly intervals, or as otherwise deemed proper by a competent physician.

For Classification for Discharge and for Prognosis

1. As a "negative sputum" case, but not necessarily arrested: Three successive twenty-four-hour concentrations at intervals of not more than a week.
2. As an "apparently arrested" case; as in no. 1 for three successive months.
3. For "arrested" cases, as in no. 1, but for six successive months.
4. For apparently cured: Concentration of a twenty-four-hour specimen at least once every three months for a period of two years.
5. Where facilities permit, a culture or animal inoculation is recommended with the concentration.
6. Gastric lavage is also recommended as an optional method.

DEMONSTRATION OF TUBERCLE BACILLI IN URINE

For routine or preliminary examinations:

1: Mix a twenty-four-hour urine specimen and pour it into a 1,000 cc. beaker or cylinder.
2: Allow to stand in an ice-box over night.
3: Pour off all but 400 cc.
4: Centrifuge this residue in eight 50 cc. centrifuge tubes for thirty minutes at high speed.
5: Pour or decant off all supernatant urine, leaving only about 1 to 1.5 cc. in each tube and combine the sediments from the eight tubes into one.
6: Direct smears should be made of sediment.
7: Treat the remainder with equal parts of 4 per cent sodium hydroxide for one hour at room temperature.
8: Shake occasionally.
9: Centrifuge for fifteen minutes at high speed.
10: Decant supernatant fluid and neutralize to phenol-red.
11: Sediment is now ready for planting on culture medium or inoculating into animals.

When catheterized specimens are available, they are to be preferred and should be studied as recommended above, except that the process should begin by centrifugation in eight 50 cc. centrifuge tubes, as given in no. 4 above.

For a final and more absolute diagnosis, catheterized ureteral specimens are recommended.

Each catheterized ureteral specimen should be worked up separately.

The sediment is centrifuged, smeared and stained directly and inoculated on culture media or injected into animals.

If a mixed infection exists, the material should be treated as described above.

Direct smears may be made, but they furnish little of either a positive or negative value.

All suspicious colonies on culture media should be inoculated into animals for confirmation.

All inoculated animals should receive 5 mg. Old Tuberculin intracutaneously after thirty days, at which time practically all positive ones will react.

DEMONSTRATION OF TUBERCLE BACILLI IN FAECES

1: Stir about 5 g. of the material in a mortar with two volumes of distilled water.
2: Add sufficient sodium chloride crystals to make a saturated solution.
3: Let stand one-half hour until coarser particles have settled to the bottom

of the mortar and a film of bacteria has formed on the surface.
4: Skim off the film with a sterile spoon.
5: Add two volumes of 4 per cent sodium hydroxide in a 50 cc. centrifuge tube.
6: Keep in an incubator for three hours and agitate frequently.
7: Centrifuge, decant and neutralize sediment.
8: Inoculate on media.

If animal inoculations are to be made, the sediment must be first washed with saline.

DEMONSTRATION OF TUBERCLE BACILLI IN PUS FROM COLD ABSCESSES, SKIN TUBERCLES OR OTHER DRAINING TUBERCULOUS LESIONS

If the lesions are open, treat the draining material the same as sputum; if closed, the material obtained by incision or aspiration should be planted on media and injected into animals without previous digestion. Whether digestion is necessary or not is left largely to the discretion of the laboratory director or physician in charge.

DEMONSTRATION OF TUBERCLE BACILLI IN PLEURAL, PERITONEAL OR OTHER SEROUS EFFUSIONS

Such effusions are handled much the same way as pus. If contamination is found or suspected, they should be treated; if they are uncontaminated, it is better to use the material directly.

DEMONSTRATION OF TUBERCLE BACILLI IN SPINAL FLUID

Secure spinal fluid in sterile tubes. Allow to stand at room temperature for twenty-four hours to permit a pellicle to form. Make direct smears from the pellicle and, if negative, culture on media. For animal inoculation mix pellicle with about 2 cc. of spinal fluid and inject. If pellicle does not form after twenty-four hours, centrifuge spinal fluid for forty-five minutes at 2,500 r.p.m. Use the sediment for smear and culture. For animal inoculation mix the remaining sediment with about 2 cc. of the original fluid and inject.

II. Red Cell Sedimentation Test

Although the sedimentation of red blood cells is strictly a nonspecific phenomenon, it is a good method to follow the course of tuberculosis after the diagnosis has been established. It is particularly useful in smaller sanatoria without the services of complete laboratory studies. For the present the Westergren or Linzenmeyer method is recommended.

WESTERGREN'S METHOD

The distance through which the red blood cells settle in uncoagulated blood in a given time is recorded in millimetres.

Pipette tubes 300 mm. in height and 2.5 mm. in internal diameter are used, with a mark 200 mm. from the bottom of the tube. By venapuncture, 1.6 cc. of blood are drawn into a 2 cc. syringe that contains 0.4 cc. of 3.8 per cent sodium citrate. Venous stasis must be avoided. After gentle agitation, avoiding air bubbles, the mixture is poured into the tube, up to the 200 mm. mark. The height of the clear plasma column is measured after one hour, and twenty-four hours. The level attained by the red cells in twenty-four hours simply gives a rough idea of the cell-plasma ratio. In healthy men the supernatant fluid column after one hour measures 3 to 8 mm., in women 5 to 10 mm.

LINZENMEYER'S METHOD

Small tubes of 5 mm. diameter, 6.5 cm. in height, are used, with two marks, one at the level of 1 cc. and the other 18 mm. below this; 0.2 cc. of 3.8 per cent sodium citrate solution and 0.8 cc. of blood are aspirated into a properly calibrated syringe, gently mixed and poured into the tube up to the 1 cc. mark. The tube is then allowed to stand upright and the time required for the upper level of the red cells to reach the 18 mm. mark is determined. This time, expressed in minutes, is the sedimentation time.

The normal sedimentation time for healthy men is from 1,200 to 1,400 minutes; for healthy women from 800 to 1,000 minutes, and during menstruation it is sometimes 600. Sedimentation times of less than 200 are usually regarded as pathological.

III. Congo-Red Test for Amyloid

Ten cc. of a 1 per cent congo-red solution are injected intravenously in the postabsorptive state. (Ampules of 10 cc. of 1 per cent congo-red solution, supplied by Hynson, Westcott and Dunning, Baltimore, Maryland, are very satisfactory.) Four minutes, and then one hour, after the injection of the dye, about 10 cc. of blood are drawn and placed in clean, dry test tubes. It is now best to wait until clotting and retraction take place. Then the tubes are centrifuged and the serum pipetted off. (Or about 10 cc. of blood is withdrawn in a dry syringe and immediately passed to a test tube containing 50 to 75 mg. of potassium oxalate, shaken well and centrifuged.) To 4 cc. of serum or plasma from each specimen 4 cc. of acetone are added. The tubes are well shaken and centrifuged at a moderate speed for about ten minutes. Removal of the proteins may also be accomplished by filtering. The clear solutions are placed in the cups of a colorimeter and compared. The four-minute specimen, used as a standard, is placed at 20 mm., while readings are made with the one-hour specimen.

Calculation:

$$100 - \frac{\text{Reading of four-minute specimen}}{\text{Reading of one-hour specimen}} \times 100 = \text{per cent absorption.}$$

From this formula the amount of dye retained by the tissues of the body during the hour is determined. The urine is also examined qualitatively for the dye by the addition of acid, which produces a blue color if congo-red is present. Lipoid nephrosis may cause a loss of all dye through the kidneys without the presence of amyloid.

Removal of all the dye in the absence of dye excretion in the urine suggests strongly the presence of amyloid.

AMERICAN TRUDEAU SOCIETY

Combined Meeting of Wisconsin and Minnesota Trudeau Medical Societies

Sixty-two physicians attended the combined meeting of the Wisconsin and Minnesota Trudeau Medical Societies held recently at Eau Claire. Forty-one were from Wisconsin, eighteen from Minnesota and one each from Illinois, North Dakota and Michigan.

The following comments on papers delivered at the Eau Claire meeting may be of interest.

In a report on 1,230 pulmonary haemorrhages of one-half ounce or more, Dr. E. P. K. Fenger of Oak Terrace, Minnesota, stated that he could not demonstrate that barometric pressure, temperature or humidity played any particular rôle as a cause of haemoptysis. Observations did reveal that there were fewer haemoptyses in recent years, probably due to greater stress on rest therapy. Pulmonary cavities were present in nearly all cases.

Drs. John D. Steele and Nathan Grossman of Milwaukee, in a paper on "Haemoptysis Due to Upper Lobe Bronchiectasis," clearly demonstrated by the use of miniature slides that ordinary X-ray films were inadequate in showing upper lobe bronchiectatic lesions. Haemoptysis was quite as common a finding in bronchiectasis as in tuberculosis and other symptoms could hardly be differentiated from tuberculosis. Repeatedly negative sputa and gastrics for acid-fast bacilli by stain, concentration examination and guinea pig inoculation are necessary before this diagnosis can be established. Lipiodol injections can usually demonstrate the dilated bronchi. Many cases are preceded by atelectasis. In a word, not all cases of upper lobe lesions, as demonstrated by haemoptysis and other symptoms and X-ray findings, are due to tuberculosis. The establishment of a diagnosis of bronchiectasis necessitates considerable study.

Dr. H. C. Hinshaw of Rochester, Minnesota, in a paper on "Hyperventilation," showed the value of carbon dioxide as a stimulant to respiration. He stated that apprehensions, fear and deep breathing at times lead to carpopedal spasm, hyperventilation seizures and even shock. In way of correction he offered (*1*) inhalation of 5 per cent carbon dioxide in oxygen mixture, or (*2*) the rebreathing of air in a paper sack—the latter being very easily available on practically any occasion.

Dr. Wm. H. Oatway, Jr., Madison, Wisconsin, and Dr. G. A. Hedberg of Nopeming, Minnesota, demonstrated interesting cases by X-ray films.

The last two papers on the program, namely, "Cardiovascular Disease Simulating Pulmonary Disease" by Dr. George C. Owen of Oshkosh, Wisconsin, and "Some Lesions Causing Widening of the Mediastinal Shadows" by Dr. C. A. Good of Rochester, Minnesota, both illustrated by lantern slides, brought to our attention the many lesions which may simulate either cardiac or pulmonary conditions or both. In this type of case it is only by complete study and careful evaluation that a correct diagnosis can be made.

VOLUNTARY TERMINATION OF ARTIFICIAL PNEUMOTHORAX[1]

A Review of 200 Cases

GEORGE F. AYCOCK[2] AND PAUL E. KELLER[3]

The induction and maintenance of artificial pneumothorax is discussed freely, and at times with boldness, in the literature. On the other hand, the approach to the voluntary termination of successful artificial pneumothorax is usually timid, with a high degree of awe, one might state.

There is a very good reason for such a general attitude, in that both the physician and patient are loathe to reverse a course which, up to the moment, has yielded satisfactory results. The popular opinion seems to have been that it is better to maintain artificial pneumothorax months or even years longer than necessary rather than run the risk of reactivation by allowing the treated lung to reëxpand prematurely.

The soundness of such a policy could not be questioned if we assume that a prolonged and indefinite collapse is necessary and not attended with any undesirable features. However, experience has taught us that an assumption of this nature is faulty, when applied generally to all cases of artificial pneumothorax. We believe some of the analyses to follow may serve to bear out this statement.

We have reviewed 200 cases of artificial pneumothorax in which there was voluntary termination of this therapeutic measure. Certain data have been accumulated as to types of cases treated, length of time under treatment and the experience of various groups of cases since completion of treatment.

For descriptive purposes these cases have been classified according to the dominant tissue reaction present and the extent of the tuberculous lesion, according to National Tuberculosis Association standards, at the time artificial pneumothorax was induced. As in a previous article (1), the dominant tissue reactions have been considered under three general groups, namely, exudative, caseous pneumonic and fibrocavern-

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ous. It is of course realized that under such a grouping there are grounds for variance of opinion as to what group certain cases should be assigned. This holds true, however, for any attempt at classification of dominant tissue reactions and the grouping we have adopted possesses the advantage of simplicity.

TABLE 1

Exudative group—far advanced lesions

DURATION OF COLLAPSE	CASES	TIME ELAPSED SINCE REËXPANSION	NUMBER OF REACTIVATIONS	PERCENTAGE OF REACTIVATIONS
Less than 18 months.....	12	12 to 80 months Average 37 months	1*	8.33
18 to 24 months.....	13	12 to 58 months Average 27 months	0	0
2 to 3 years.....	36†	12 to 177 months Average 45 months	2‡	5.6
3 to 4 years.....	11	12 to 67 months Average 38 months	1§	9.1
4 years or more.....	11	22 to 71 months Average 41 months	0	0

* This case showed reactivation of original lesion 55 months after completion of reexpansion.

† Four of these cases have been completely reëxpanded for a period in excess of ten years.

‡ One case became reactivated 55 months after completion of reëxpansion and is still under treatment. Another, a bilateral case, showed a mild reactivation in the left mid-lung area, 28 months after completion of reëxpansion. This reactivation cleared up within one year and the case has again been carried as arrested for a period in excess of one year.

§ This case showed reactivation 12 months after completion of reëxpansion.

According to this grouping, the cases studied were divided as follows:

Exudative	179
Caseous pneumonic	3
Fibrocavernous	18

This review includes only those cases in which reëxpansion has been completed for one year or more and only those cases in which a reasonably satisfactory follow-up has been maintained since the completion of reëxpansion.

Three factors of immediate interest in such a group of cases naturally

TABLE 2

Exudative group—moderately advanced lesions

DURATION OF COLLAPSE	NUMBER OF CASES	TIME ELAPSED SINCE REËXPANSION	NUMBER OF REACTIVATIONS	PERCENTAGE OF REACTIVATIONS
Less than 18 months.....	34	12 to 178 months Average 46 months	1*	2.9
18 to 24 months.....	22	12 to 138 months Average 41 months	0	0
2 to 3 years.....	18	12 to 134 months Average 45 months	1†	5.6
3 to 4 years.....	9	14 to 58 months Average 40 months	1‡	11.1
4 years or more.....	2	24 and 28 months	1§	50.0

* Reactivation occurred 30 months after completion of reëxpansion.

† Reactivation occurred 33 months after completion of reëxpansion.

‡ Reactivation occurred 14 months after completion of reëxpansion.

§ Reactivation occurred 28 months after completion of reëxpansion. This reactivation cleared up within 8 months and lesion has been considered arrested for 18 months.

TABLE 3

Exudative group—minimal lesions

DURATION OF COLLAPSE	NUMBER OF CASES	TIME ELAPSED SINCE REËXPANSION	NUMBER OF REACTIVATIONS	PERCENTAGE OF REACTIVATIONS
Less than 18 months.....	7	15 to 78 months Average 34 months	0	0
18 to 24 months.....	2	24 and 35 months	0	0
2 to 3 years.....	2	12 and 50 months	1*	50.0

* This case showed reactivation 12 months after completion of reëxpansion.

TABLE 4

Caseous pneumonic group

DURATION OF COLLAPSE	NUMBER OF CASES	TIME ELAPSED SINCE RE-EXPANSION	NUMBER OF REACTIVATIONS	PERCENTAGE OF REACTIVATIONS
		months		
Far Advanced Lesions				
3 to 4 years.....	1	40	0	0
4 years or more.....	1	80	0	0
Moderately Advanced Lesions				
18 to 24 months.....	1	58	0	0

suggest themselves, namely, duration of collapse, time elapsed since completion of reëxpansion and incidence of reactivation. Accordingly, analyses of cases have been made on this basis for the dominant tissue reaction groups as previously outlined. These analyses are given in tables 1, 2, 3, 4 and 5.

TABLE 5

Fibrocavernous group

DURATION OF COLLAPSE	NUMBER OF CASES	TIME ELAPSED SINCE REËXPANSION	NUMBER OF REACTIVATIONS	PERCENTAGE OF REACTIVATIONS
Far Advanced Lesions				
18 to 24 months	2	21 to 24 months Average 22 months	0	0
2 to 3 years	5	24 to 74 months Average 38 months	0	0
3 to 4 years	4	12 to 34 months Average 25 months	1*	25.0
4 years or more	2	21 and 202 months	0	0
Moderately Advanced Lesions				
18 to 24 months	3	14 to 73 months Average 42 months	1†	33⅓
2 to 3 years	2	68 and 137 months	0	0

* This case suffered a severe reactivation 22 months after completion of reëxpansion and died.

† This case had reactivation of lesion 14 months after completion of reëxpansion.

CRITERIA FOR REËXPANSION

The condition of the patient and the lesion under treatment, as determined by the clinical course, roentgenological findings, sputum analysis and erythrocyte sedimentation rate, has been the prime factor in arriving at a decision to voluntarily terminate artificial pneumothorax in a majority of the cases constituting this group. The element of a fixed period of collapse for a given type of lesion, regardless of the condition of patient and lesion, has been accorded little importance. The time element has been applied only in so far as it relates to the closure of cavities. It has been the policy to delay the initiation of reëxpansion until a period of

one year has elapsed after the complete closure of cavities, as determined by roentgenological appearance and negative sputum.

Clinical course: It goes without saying that the patient should be free from toxaemic symptoms referable to the tuberculous process before termination of pneumothorax. The same may be said of cough and expectoration in a majority of cases. However, there are cases with considerable fibrous residuals, associated with bronchitis, and at times with bronchiectasis, in which cough and expectoration will not disappear, regardless of the state of the tuberculous lesion.

The weight of the patient under collapse therapy is another factor susceptible to varied interpretations. While it is usual to expect the successful case of artificial pneumothorax to gain weight, or at least to maintain it, several cases in this group, notably some bilateral cases, not only failed to gain weight but showed small losses during the maintenance of collapse. Otherwise they followed a favorable course. These same cases showed a check in their weight loss or an actual gain in weight on reëxpansion. Such cases usually would be annoyed by occasional nausea and anorexia. These symptoms could not be ascribed to pressure on the hemidiaphragm, on the treated side, with consequent encroachment on the abdominal viscera, because in most of the cases under discussion this condition did not obtain.

Roentgenological findings: In those cases of the exudative group which cleared up, leaving little or no residuals, the problem of roentgenological control of reëxpansion was relatively simple. In most of the cases under study an attempt had been made to carry on only a partial collapse, even of the diseased area of the treated lung. Under such conditions of collapse it is often possible to form a reasonable estimate of the state of the lesion, roentgenologically, before reëxpansion is initiated. With gradual reëxpansion, which has been accomplished in all these cases under review, the roentgenogram will usually tell its final story of the treated lung before reëxpansion is complete and while an intrapleural space is still present. As to our meaning of gradual reëxpansion, it might be proper to state that the period covered by this phase of the procedure, of course, varies in different cases, but that reëxpansion was seldom accomplished in less than three months after its initiation.

Those cases leaving more in the way of fibrous residuals increase the perplexity of the reëxpansion problem. Such cases often show various types of interlacing shadows, many at times suggesting the presence of patent cavities. It is usually necessary, when confronted with reëxpan-

sion problems of this nature, to take roentgenograms from several angles, lateral and oblique. The stereo-roentgenogram is a necessity in such situations and will often clear up confusing points at issue. Laminagraphy gives promise of material help in some of these cases.

It is most important to correlate all other findings, clinical and laboratory, with roentgenological findings, before arriving at a final decision.

Often the greatest aid in formulating an accurate estimate of the situation in a given case is the knowledge of what has transpired since artificial pneumothorax was instituted. If serial roentgenograms, made at sufficiently frequent intervals, are augmented by fluoroscopic knowledge acquired before and after refills, one usually may feel very well justified in arriving at a definite conclusion as to the condition of the lesion in the case under study. This presupposes that the case be followed by the same physician, or a small group of physicians, from the inception of collapse to its termination. According to our views this constitutes the best plan of management for artificial pneumothorax.

Sputum analysis: Our plan of sputum examination prior to completion of expansion presupposes that repeated specimens have been negative, on direct smear, for a period of one year. When reëxpansion is almost complete, but with a definite intrapleural space still present, five more direct smears are examined and a culture is then made. Recently we have added the procedure of culture of stomach washings in cases showing appreciable residuals. When reëxpansion is complete another sputum culture is an added check on previous findings.

Erythrocyte sedimentation rate: A low erythrocyte sedimentation rate is desired, well below 10 mm. in sixty minutes (Cutler method). Of more significance, in our opinion, is a rate definitely and consistently lower in a given case on completion of treatment than that noted when treatment was instituted.

LENGTH OF TIME OF COLLAPSE

It must be admitted the period of collapse in most of our cases was well under the minimum recommended by a majority of the writers of the present time. It will be noted that slightly over 60 per cent of the far advanced exudative cases were completely reëxpanded within a period of three years, while in approximately 30 per cent of the same type of cases reëxpansion was completed within a period of two years. A closer study of each group, according to the length of time of collapse and the incidence of reactivation in reëxpanded cases, may be of value in arriving at a conclusion as to whether or not the time element of col-

lapse, *per se*, is a vital factor in determining the end-results of artificial pneumothorax.

In the far advanced exudative group, we find a reactivation incidence of 8.3 per cent in the series of 12 cases which were under collapse less than eighteen months. The series of 11 cases, which were under collapse for a period of from three to four years, more than twice as long, showed a reactivation incidence of 9.1 per cent. No reactivations were noted in the series of 13 cases under collapse for a period of from eighteen to twenty-four months and in the series of 11 cases under collapse for a period of four years or more. In this comparison of the different series, each containing nearly the same number of cases, there is nothing in the reactivation incidences to suggest that the cases under collapse for the longer periods of time were less likely to show reactivation than those under collapse for the shorter periods of time, unless we limit our comparison to cases of the shortest collapse period with those of the longest collapse period. The objection might be raised that 11 to 13 cases in each series constitute too small a number for a worth while study of reactivation incidence. This objection can be met partially by reducing the number of series to three in the far advanced exudative group. By combining the first two series we will have a total of 25 cases under collapse for a period less than two years, with a reactivation incidence of 4 per cent. If we leave the series under collapse for a period of from two to three years as it was, we have 36 cases with a reactivation incidence of 5.6 per cent. The third series, then, will be all cases which remained under collapse for a period in excess of three years, or a total of 22 cases, with a reactivation incidence of 4.5 per cent. Certainly there is nothing in the reactivation incidence, according to this grouping, to justify a conclusion that there is a definite relation between the period of collapse and the incidence of reactivation after expansion.

This point is more clearly emphasized when we consider the moderately advanced exudative group. If we eliminate the series of 22 cases remaining under collapse for a period of from eighteen to twenty-four months in which no reactivations occurred, we find a progressive increase in the reactivation incidence with each increment of period under collapse. In short, the highest reactivation incidence occurred in that portion of the cases in this group remaining under collapse for the longest periods of time. Here again the small number of cases under collapse for the periods of from three to four years and four years or more makes their isolated reactivation incidence misleading.

However, if we combine the last three series, which would include all

cases of this group under collapse for a period exceeding two years, we have a total of 29 cases, with 3 cases showing reactivation. This reactivation incidence of 10.3 per cent is still well above that experienced in the cases under collapse for a period less than two years.

These figures, of course, do not prove that an increased period of collapse, *per se*, will lead to a higher reactivation incidence. Other factors must be considered also. However these figures do offer some support to the policy of determining the time of reëxpansion on the basis of the condition of the patient and treated lesion, rather than upon some arbitrary number of years of collapse.

The number of cases in each series among the minimal classification of the exudative group and all classifications of the caseous pneumonic and fibrocavernous groups is too small for the percentage incidence of reactivation therein to indicate any definite trend.

It is a fact worthy of note that no reactivations occurred in any of the cases under study within a period less than twelve months after completion of reëxpansion. In most of the cases showing reactivation, more than two years had elapsed since completion of reëxpansion. Certainly the idea, often expressed, that reactivation is caused by the "stretching" of lesions incident to the act of reëxpansion, cannot be applied here. As a matter of fact, our experience in this group of cases, as well as in others we have observed, leads us to believe that reëxpansion, *per se*, has little or nothing to do with reactivation of tuberculous lesions. If the healing process has advanced to a satisfactory degree, reëxpansion is not going to retard this process or alter its course unfavorably. We cannot escape the implication that cases showing signs of activity immediately upon completion of reëxpansion have never reached a state of arrestment.

The percentage incidence of reactivations and the time of occurrence of reactivations in the entire group of cases under study offer no essential variations from the experience at this hospital during the last twenty years with reference to reactivations in cases which have been adjudged arrested or apparently cured under treatment other than collapse therapy. In cases so treated no one is surprised if reactivations occur, within five years, in from 5 to 10 per cent of cases adjudged arrested or apparently cured. It seems reasonable to assume, then, that if a reactivation incidence no larger than this occurs in cases of reëxpanded artificial pneumothorax, the act of reëxpansion has exerted no appreciable influence as a reactivating factor.

It would appear pertinent to add in this connection that cases remain-

ing under collapse for indefinite periods of time may show reactivations or extensions. For example, during the last twelve years, 30 cases of permanent artificial pneumothorax have accumulated at Fitzsimons General Hospital through no intention on the part of the physicians directing the treatment. The periods of collapse in this group varies from five to twelve years. During the last two years 3 reactivations or "spreads" have occurred. One had been under collapse for a period of five years, another for a period of seven years and a third for a period of eleven years. Thus, in this group of permanently collapsed cases, the reactivation incidence of 10 per cent equals or exceeds that of reëxpanded cases.

Any discussion of the duration of collapse in artificial pneumothorax will naturally suggest the consideration of the disadvantages of prolonged or indefinite periods of collapse. Aside from the inconvenience and expense to the patient, the chief disadvantage is the greater likelihood of troublesome and serious complications or sequelae.

It may be taken for granted that, as long as a pneumothorax space is present, the hazard of such complications as effusion and superimposed spontaneous pneumothorax exists. While it is true that according to most published statistics these complications show their greatest incidence during the first twelve months of artificial pneumothorax, no case may be considered free from the likelihood of such complications after that period.

In some cases of long standing artificial pneumothorax, where no effusion has been demonstrated, there is noted a marked thickening of the visceral pleura, with an attendant fixation of the collapsed lung. Perhaps such thickening is a result of the dry pleurisy described by Lindblom, reference to which is made by Farber and Lincoln in their discussion of cases of unexpandable lung (2).

Pleural thickening, whether the result of an effusion or dry pleurisy of long standing, may be attended by interstitial pulmonary fibrosis in the collapsed lung, with partial or total loss of its expansile properties. As a result of this train of events, the fixed or unexpandable lung develops. The tragedy of such a development is that the whole of the treated lung usually has lost its expansile property, when, as a matter of fact, the distribution of the lesion for which artificial pneumothorax was instituted in many cases was confined principally to an upper lobe. Thus, an entire lung has been thrown out of function permanently in the treatment of a lesion confined for the most part to its upper third.

When this state of affairs ensues, air is still absorbed from the intrapleural space, though with less rapidity than in the presence of a permeable pleura. As a result the intrapleural pressure diminishes, or, in other words, becomes more highly negative. The collapsed lung, having lost its expansibility, cannot expand to "meet" this high negative pressure. Under such circumstances, unless refills are given with sufficient frequency to overcome partially this high negative pressure, there is likely to be a marked retraction, involving the mediastinal structures, toward the treated side, the development of a massive effusion, or both of these untoward accidents may occur. As a matter of fact their occurrence cannot be invariably obviated by continued refills.

The fixed or unexpandable lung, then, not only has lost its function, but is frequently attended by such marked retraction as to cause mediastinal distortion. The combination of these two factors constitutes the potentiality for increased pulmonary tension and thus a perfect build-up for right-sided heart failure is created.

Our observations in such cases are in agreement with those of Brumfiel (3), who believes that the loss of functioning lung tissue alone does not often result in right-sided heart failure, unless this loss be excessive. On the other hand, marked mediastinal distortion associated with relatively little loss of functioning lung tissue is often associated with manifestations of right-sided heart failure.

There appears to be no constant sign of impending right-sided heart failure in these cases. It is true that in some the electrocardiogram will show a right axis deviation or, occasionally, the right ventricular shadow may appear enlarged on the roentgenogram. However, in our experience, most cases have not shown any conclusive signs until the actual development of right-sided heart failure.

It is the common experience that most cases with mediastinal distortion may go along for some years with little discomfort other than mild tachycardia or dyspnoea on more than slight exertion, provided conditions are favorable. However, under the influence of unusual stress, such as an acute respiratory infection or a major surgical procedure, decompensation often ensues.

At present a study is in progress at this institution, the object of which is to correlate antemortem clinical and laboratory findings with postmortem findings in a sufficiently large group of these cases to justify definite conclusions.

Some authors appear inclined to the opinion that right-sided heart failure occurs only in cases with preëxisting myocardial degenerative

changes resulting from toxaemia incident to the tuberculous process. If this be true, it would seem from our preliminary study that more cases of tuberculosis have suffered degenerative myocardial changes than we have been taught to expect.

It is felt that sufficient evidence is now at hand to form a basis for the opinion that right-sided heart failure is a much more important factor in chronic pulmonary disease associated with mediastinal distortion than has been generally ascribed to it. If this opinion is borne out by further study, then it would appear that due consideration should be given the problem of mediastinal distortion in cases under artificial pneumothorax. All known factors in its production should be obviated in so far as it is possible to do so. Certainly the factor of prolonged and indefinite collapse can be obviated in many cases. At least, we should recognize the fact that in these cases of prolonged collapse we may be faced with the decision as to whether probable beneficial effects of continued collapse on the tuberculous process are sufficiently important to justify a course which may render patients under treatment potential candidates for right-sided heart failure.

Unquestionably there are cases in which the decision to take the chance of right-sided heart failure is justified in the face of immediate danger of an uncontrollable tuberculous extension if a satisfactory collapse is terminated prematurely. However, we feel that all patients under artificial pneumothorax should not be subjected to this risk indiscriminately, just for the sake of adhering to an arbitrary schedule of collapse.

SUMMARY

Two hundred reëxpanded cases of artificial pneumothorax have been studied. These cases were classified according to dominant tissue reactions existing prior to the induction of artificial pneumothorax, namely, exudative, caseous pneumonic and fibrocavernous.

One hundred and seventy-nine cases were classified as exudative, 3 as caseous pneumonic and 18 as fibrocavernous.

Periods elapsed since completion of expansion range from one to sixteen years.

For purposes of statistical study, the duration of collapse has been considered under five periods, namely, less than eighteen months, eighteen to twenty-four months, two to three years, three to four years, and four years or more.

The far advanced and moderately advanced series of the exudative group comprise 168 cases of the total of 200 reviewed.

The reactivation incidence in the far advanced exudative series indicates that the time element of collapse, *per se*, does not have any bearing upon future reactivation after completion of reëxpansion. As examples, the experience in the several subseries of this group will be cited:

Out of 12 cases under collapse for a period of less than eighteen months, one case showed a reactivation of the original lesion fifty-five months after completion of reëxpansion. This represents a reactivation incidence of 8.3 per cent. Comparing this with a subseries of 11 cases under collapse for a period of three to four years, we find one case showed reactivation twelve months after completion of reëxpansion or a reactivation incidence of 9.1 per cent.

A series of 13 cases under collapse for a period of from eighteen to twenty-four months showed no instances of reactivation. The same was true of a subseries of 11 cases under collapse for a period of four years or more.

The largest subseries in this group, 36 cases under collapse for a period of from two to three years, showed 2 cases of reactivation or a reactivation incidence of 5.6 per cent. This reactivation incidence is only slightly above that of the far advanced exudative series as a whole—a total of 83 cases, among which 5 showed reactivation, giving a reactivation incidence of 4.8 per cent.

In the moderately advanced exudative series, the absence of any relation between the duration of collapse and reactivation after reëxpansion is even more clearly emphasized.

According to reactivation experience in the moderately advanced exudative series, those cases under collapse for the shortest period of time fared better after completion of reëxpansion than those under collapse for longer periods of time. This, of course, must not be interpreted as implying that the longer periods of collapse, *per se*, constitute a factor in the occurrence of reactivations.

Experience in the group of cases under study fails to show any connection between the act of reëxpansion and subsequent reactivations. No case showed reactivation within a period of less than twelve months following completion of reëxpansion. Most of the reactivations occurred at periods in excess of two years after completion of reëxpansion. The incidence and time of reactivations have in all essential respects been the same in this group of reëxpanded pneumothorax cases, as in those cases discharged from Fitzsimons General Hospital as arrested, or apparently cured, without having received any form of collapse therapy.

Prolonged and indefinite periods of collapse under artificial pneumothorax present certain very definite disadvantages. Aside from the added inconvenience and expense to the patient, the chief disadvantage is the likelihood of development of serious complications. Pneumothoraces of long standing, with or without the complication of effusion, sometimes show marked thickening of the visceral pleura, with a fixation of the collapsed lung, resulting in what has been termed the "unexpandable lung." Right cardiac hypertrophy and failure in such cases are assuming increased importance as a grave end-result in chronic pulmonary disease, associated with mediastinal distortion, and deserve further serious study.

SUMARIO

Este estudio comprende 200 casos de reexpansión de un neumotórax terapéutico, clasificados según las reacciones histológicas que predominaban antes de aplicarse la colapsoterapia, o sean: exudativas, neumocaseosas y fibrocavernosas.

Ciento setenta y nueve casos fueron clasificados como exudativos, 3 como neumocaseosos y 18 como fibrocavernosos.

El período de tiempo transcurrido desde que se completó la expansión varió de uno a dieciséis años.

Para fines estadísticos, se ha estudiado la duración del colapso en cinco grupos, a saber: menos de dieciocho meses, dieciocho a veinticuatro meses, dos a tres años, tres a cuatro años, y cuatro años o más.

La serie muy avanzada y moderadamente avanzada del grupo exudativo comprende 168 casos del total de 200 estudiados.

La frecuencia de la reactivación en la serie exudativa muy avanzada indica que el elemento tiempo en sí mismo no guarda la menor relación con la reactivación futura después de completarse la reexpansión. Como ejemplo, cítanse las siguientes observaciones en las varias subseries del grupo:

De 12 casos en que el colapso duró menos de dieciocho meses, un caso reveló una reactivación de la lesión primitiva a los cincuenta y cinco meses de completarse la reexpansión, lo cual representa un coeficiente de 8.3 por ciento.
Comparando este resultado con otra subserie de 11 casos en que el colapso ha durado de tres a cuatro años, obsérvase un caso de reactivación a los doce meses de completarse la reexpansión, o sea un coeficiente de 9.1 por ciento.
En una serie de 13 casos en que el colapso ha durado de dieciocho a veinti-

cuatro meses, fno se observó ninguna reactivación. Lo mismo reza con otra subserie de 11 casos en que el colapso ha durado cuatro años o más.

La subserie más numerosa del grupo, o sean 36 casos de colapso durante un período de dos a tres años, reveló dos casos de reactivación, o sea un coeficiente de 5.6 por ciento. Este coeficiente de reactivación sólo supera ligeramente el de la serie exudativa muy avanzada en conjunto, o sea un total de 83 casos, de los cuales 5 revelaron reactivación, o sea un coeficiente de 4.8 por ciento.

En la serie exudativa moderadamente avanzada, aparece aun mejor recalcada la falta de toda relación entre la duración del colapso y la reactivación.

Según las observaciones relativas a la reactivación en la serie exudativa moderadamente avanzada, los casos en que el colapso había durado menos lo pasaron mejor después de completarse la reexpansión que aquéllos en que la colapsoterapia había durado más tiempo. Por supuesto, no debe interpretarse esto como denotando que los períodos más prolongados de colapso constituyan en sí mismos un factor en la aparición de reactivación.

Las observaciones realizadas en el grupo de casos estudiados no revelan relación alguna entre el acto de la reexpansión y las reactivaciones subsecuentes. Ningún caso mostró reactivación en menos de doce meses después de completarse la reexpansión. La mayor parte de las reactivaciones se presentaron en períodos que excedían dos años después de completarse la reexpansión. La frecuencia y período de tiempo en que se presentaron las reactivaciones fueron en todos los puntos esenciales idénticos en este grupo de reexpansión del neumotórax a los observados en los casos dados de alta del Hospital General Fitzsimons como estacionados o aparentemente curados, sin haber recibido colapsoterapia en forma alguna.

Los períodos prolongados e indefinidos de colapso con el neumotórax terapéutico, entrañan ciertas desventajas muy precisas. Aparte de los mayores inconvenientes y gastos que acarrean al enfermo, la principal desventaja consiste en la probabilidad de que sobrevengan complicaciones graves. Un neumotórax muy antiguo, complicado o no con derrame, revela a veces decidido espesamiento de la pleura visceral y fijación del pulmón aplastado, dando por resultado lo que se ha llamado "pulmón inexpandible." La hipertrofia e insuficiencia del corazón derecho que se observan en dichos casos, van revistiendo mayor importancia como grave resultado terminal en las neumopatías crónicas, asociándose con

desfiguración del mediastino, y siendo acreedoras a ulteriores estudios detenidos.

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PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS[1]

Results in a Follow-up Study of 117 Cases

ALLAN HURST AND SOLOMON SCHWARTZ

Though begun about sixty years ago, pneumothorax therapy in pulmonary tuberculosis did not become a popular procedure until more than thirty years later. During that time, there has been an advance in knowledge as to indications, particularly in the so-called progressive minimal case, as well as in bilateral cavitary disease. After the treatment has been continued satisfactorily for some years, the problem arises as to the optimum time for discontinuation. There is complete lack of agreement in this regard, for various investigators suggest markedly different periods. Neumann (1) has suggested a collapse lasting two years, and others recommend that the treatment be continued indefinitely. Some recent workers insist that the duration of the treatment depends upon the character and extent of the original lesion with a minimum collapse of five years.

There have been few reports in the literature in regard to end-results of pneumothorax therapy. In addition, most investigators have included cases with ineffective collapse which were discontinued very early in the course of therapy. Because of the improper inclusion of these cases, there has resulted considerable confusion.

OBSERVATIONS

The present study consists of 117 pneumothorax cases, all of whom have had collapse therapy for a minimum of two years. In a small group, a little less than 10 per cent, the treatment was discontinued involuntarily. They have been included however, because they conformed to the minimum length of therapy. All cases were treated in two of the large Department of Health Clinics in New York City. They were previously treated in the tuberculosis sanatoria and hospitals of New York State for the most part where they remained for at least six months.

[1] From the Bureau of Tuberculosis, Dr. Herbert R. Edwards, Director, Department of Health, New York City.

On admission to the clinic, they were considered to be cases of effective collapse, that is, the sputum had been rendered negative. The patients were almost invariably of quite low economic levels, many living on subsistence diets.

In the clinic, the pneumothorax was continued at regular intervals and examinations and X-ray films were done periodically. Sputum studies, both by concentrated method and by gastric lavage were done frequently, particularly just before and after cessation of therapy. About two years ago, the use of the erythrocyte sedimentation test was discontinued. Work done by Pessar and Hurst showed that there was too great a discrepancy between sedimentation rate and clinical condition of the patient, as determined by X-ray, weight, temperature and work ability, to warrant much reliance to be placed upon it.

In only a little more than two-thirds of the cases were we able to secure the original X-ray films prior to the institution of collapse therapy. In the remainder we were forced to accept a description of the X-ray findings forwarded to us from the sanatoria and hospitals.

After it was decided to discontinue a case, pneumothorax refills were stopped abruptly. Each was watched carefully with frequent X-ray examinations and sputum studies during the reëxpansion period. In many, small pneumothorax pockets and other highlights appeared which were difficult to distinguish from cavities. When these were seen, we had to rely upon the results of serial X-ray films and sputum examinations for final decision. In no instance was it necessary to resume the pneumothorax treatment during reëxpansion because of suspicious X-ray shadows.

For convenience, we have grouped our cases, insofar as their present status is concerned, into "dead," "active," "arrested" and "apparently cured." The last three named will be defined to avoid misunderstanding, although we have attempted to stay as close as possible to the definitions of the National Tuberculosis Association.

Active: Any case showing a positive sputum or unstable lesion by X-ray. Where patients showed significant symptoms without X-ray changes, they were carefully observed until a definite diagnosis of activity could be made.

Arrested: Following complete reëxpansion, a negative sputum, a stable lesion by X-ray, no significant complaints and a fair degree of physical activity for a minimum of six months. Because of the question of physical activity, many cases have been included in this group who would

otherwise be added to the last, apparently cured group, because of their inability to work. For the most part, this has been due to dyspnoea on exertion, an end-result of the retraction and pulmonary fibrosis following pneumothorax therapy. Similarly, 4 cases of localized tuberculous empyemata have been added although they fit into the cases of cured by definition.

Apparently cured: Following discontinuation of pneumothorax, negative sputum, stabilized lesion on X-ray, and the ability to work for not less than two years.

In discussing our results, we have grouped together the dead and active cases, for comparison with the total of arrested and apparently cured cases. The average follow-up of all cases, except those dead or in

TABLE 1

Present status of cases according to duration of pneumothorax

STATUS	DURATION OF PNEUMOTHORAX								Total Cases
	2 years		3 years		4 years		5 years and over		
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Apparently cured	14	63.7	45	65.2	15	75.0	5	83.3	79
Arrested	3	13.6	9	13.0	4	20.0	—	—	16
Active	5	22.7	14	20.3	1	5.0	1	16.7	21
Dead	—	—	1	1.5	—	—	—	—	1
Total	22	100.0	69	100.0	20	100.0	6	100.0	117

a hospital since discontinuation of therapy, was four years. The minimum was one and one-half years, and the maximum six years and two months.

Age: The youngest patient was sixteen, and the oldest fifty-eight years of age. The greatest number of cases were between twenty and thirty years of age. We were unable to find any difference in the incidence of breakdowns in any particular group.

Sex: There were 53 males and 64 females. Again the incidence of breakdowns was not remarkably different in the two series.

Race: Since the majority of the cases (109) were of the white race, it was impossible to draw any comparative conclusion.

Duration of pneumothorax is best shown in table form. The duration of pneumothorax in years has been plotted against the present status of the individual case. There will be a slight variation in the figures as

compared with those shown later in the table of relapsed cases. This is due to the fact that in table 1 we are discussing the present status, and a few of the relapse cases have since become arrested or cured.

There were 12 cases of pneumothorax expanded involuntarily that are included in the series. They were divided as follows:

a: Obliterative pleuritis: 5 cases. Length of pneumothorax was from two to three years and all are apparently cured.
b: Massive effusion: 2 cases. Pneumothorax of two years' duration. Both cases had contralateral breakdowns, one of whom is active and the other arrested.
c: Delinquency: 4 cases. Pneumothorax was continued for a little over two years to more than four years. Of the 4 cases, 2 are arrested, one is apparently cured and one is active with a homolateral breakdown.
d: Temperature reaction: one case. Length of collapse was more than three years and the patient is apparently cured.

Duration of the disease by symptoms prior to institution of pneumothorax was analyzed as to results of therapy. Symptoms of less than six months, from six to twelve months and more than one year were compared. It was surprising to find that the incidence of breakdowns was least in those having symptoms for more than one year. It would appear from this that the more chronic the case, the better the results from therapy, once a good collapse is secured.

The interval of conversion of sputum was similarly studied. Here the various classes were charted against conversion groups of less than three months, from three to six months and more than six months. The comparison of these three groups showed little or no difference in the end-result. It may be concluded that once the collapse becomes effective enough to render the sputum negative, the result is uniformly the same regardless of the time interval.

Probably the most important single factor of pneumothorax is the character of collapse as influenced by adhesions. For convenience we divided our cases into three groups as follows (this represents a modification of the four groups of Hjaltested and Törning (2):

1: No adhesions to apex or costal wall. Mediastinal or diaphragmatic adhesions were not included since we had no cases of basal cavity.
2: Circumscribed or isolated apical or costal adhesions, also called "band" or "string" adhesions.
3: Diffuse pleural symphsis or multiple costal adhesions.

In other reports on the results of pneumothorax therapy, the character and extent of the original pulmonary lesion was that of the National Tuberculosis Association. We have divided our cases, as seen in table 3, into unilateral and bilateral. Under bilateral, they have been further subdivided into significant and insignificant lesions. An insignificant lesion will be defined as a small fibrotic nodule or strand, or calcifications

TABLE 2

Present status of cases grouped according to character and extent of adhesion

STATUS	GROUP 1		GROUP 2		GROUP 3		TOTAL CASES
	Number	Per cent	Number	Per cent	Number	Per cent	
Apparently cured	22	81.5	42	66.7	15	55.6	79
Arrested	2	7.4	9	14.3	5	18.5	16
Active	3	11.1	11	17.5	7	25.9	21
Dead	—	—	1	1.5	—	—	1
Total	27	100	63	100	27	100	117

TABLE 3

Present status of cases according to character of original lesion

STATUS	UNILATERAL		BILATERAL				TOTAL CASES
			Significant		Insignificant		
	Number	Per cent	Number	Per cent	Number	Per cent	
Apparently cured	44	71.0	29	65.9	6	60	79
Arrested	11	17.7	4	9.1	1	10	16
Active	7	11.3	10	22.7	3	30	20*
Dead	—	—	1	2.3	—	—	1
Totals	62	100	44	100	10	100	116*

* One active case is excluded from total, as pneumothorax was induced in a foreign country and original X-ray findings could not be secured.

at the apex or localized in the lung, recognized as other than a healed primary infection.

Relapses: These will be discussed separately under relapses occurring on the side of the pneumothorax, homolateral, and those on the opposite or contralateral side.

There were 12 cases of homolateral relapse in the series of 117 cases, or approximately 10 per cent. Of the 12 cases, 3 relapsed after six months, 4 after one year and 6 after more than two years. As to the duration of pneumothorax, the best results were secured in the group with

pneumothorax for more than four years. Two became active in the two-year group, nine in the three-year group, and only one in the four-year group. In the study made for the type of lesion found in the homolateral relapses, we could only use 11 of the 12 cases, because one had had her pneumothorax induced in a foreign country and we were unable to secure the original X-ray films. There were 6 unilateral and 5 bilateral cases. As to the character of collapse, it is to be noted that there were no relapses in the ideal group 1. There were 7 relapses in group 2 and 5 in group 3.

Relapses were diagnosed on the basis of increasing symptoms, X-ray changes or positive sputum. Among these 12 cases, we have included one case that developed an empyema two years after reëxpansion. He subsequently had a thoracoplasty and is now arrested.

TABLE 4

Present status of all relapsed cases

	APPARENTLY CURED	ARRESTED	ACTIVE	DEAD	TOTAL
Homolateral		3	9		12
Contralateral	2	2	12	1	17

In the contralateral group, there were 17 cases. Of these, the majority of relapses were in the nature of small exudative lesions which could be treated by simple rest regimen. We have not included those contralateral lesions which were a problem during pneumothorax therapy since we are dealing only with results following reëxpansion. The interval of breakdown was not extraordinary in any time grouping, since about equal numbers were found from six months up to three years after reëxpansion.

COMPLICATIONS

There were 2 cases of rheumatic heart disease, both of whom went through their pneumothorax therapy satisfactorily. Three cases of diabetes mellitus, all well controlled by diet and insulin, were successfully treated and are in the apparently cured or arrested group. Five patients became pregnant during pneumothorax therapy and delivered without mishap. One of these 5 also went through a pregnancy following reexpansion. All 5 cases with 6 pregnancies are well. One other patient became pregnant after reëxpansion and reactivated her pulmonary lesion after reëxpansion one year after delivery.

Although not a complication, it is to be noted that in the series of

117 cases, there were 3 cases with bilateral pneumothorax, all well and in the "apparently cured" group.

There were 4 cases of localized tuberculous empyemata which were discussed previously. These patients are all working and really belong in the "apparently cured" group by virtue of definition. They have been placed in the "arrested" group to avoid criticism, although we feel that the pulmonary lesion is well healed, and the small collection of pus is the remains of a burned-out infection and does not represent a therapeutic problem.

There was one case of haemothorax and 11 cases of massive *ex-vacuo* effusions treated conservatively for the most part.

Bronchiectasis was demonstrated with lipiodol in 4 cases, although we feel that there were probably many more cases.

Under adjuvant procedures, there were 2 thoracoplasties, one for a contralateral lesion, and one for empyema on the homolateral side mentioned previously. There were also 3 phrenic nerve operations, and 4 cases of intrapleural pneumonolysis.

DISCUSSION

It has been estimated that the 117 cases here discussed represent about 1,000 cases of pulmonary tuberculosis in institutions for whom pneumothorax was originally planned. Of these 1,000 cases, only 25 to 30 per cent will be satisfactorily induced. Massive effusions, empyema, progressive tuberculosis and other complications will eliminate many more. After discharge from the hospital and sanatorium, similar complications, as well as obliterative pleuritis, will again bring the total down markedly. Thus it must be emphasized that we have discussed here the results of the "good" cases, arrived at by a so-called "self-weeding" process. Viewed from this light one would have expected far better results.

There are still advantages of a successful pneumothorax as compared to conservative methods of treatment. Only one of our patients is dead and the remainder are alive, an average of seven years after induction of pneumothorax. Similarly Eglee and Jones (3) had only one death in 100 reëxpanded pneumothoraces followed an average of 3.2 years. Half of 20,000 open cases were dead in five years (Berg (4)). Barnes and Barnes (5) found that the average duration of life of positive sputum cases was thirty months.

Patients in whom pneumothorax has been tried and failed have a very high mortality rate. Packard (6) found a mortality rate of 60 per cent

at the end of two years in patients in whom pneumothorax had been tried unsuccessfully. Sinding-Larsen (7) had a mortality rate of 22 per cent in 142 pneumothorax failures. In contrast, Peters *et al.* (8), Packard (9) and Sinding-Larsen (7) had a mortality rate of 11 per cent or less in effective pneumothorax cases.

A problem in pneumothorax therapy is when to discontinue pneumothorax. Packard's (9) best results were in pneumothorax maintained two years or more. Dufault and Laroche's (10) best results were in pneumothorax maintained for over three years. Our figures show a sharp dividing line once pneumothorax is maintained for four years or more. Of 20 cases who had pneumothorax maintained for four to five years, only one is active. We do not feel that a contralateral relapse can be attributed to or explained by a pneumothorax. Of 12 homolateral relapses only one occurred in a patient who had a pneumothorax maintained for four to five years. This would suggest that pneumothorax maintained for a period of at least four years should produce a more favorable outcome, with fewer relapses than one maintained for a shorter period.

We did not find any particular difference in the end-results of young or old patients, in female or male patients, or between a short history or a long history of disease. Our length of disease was determined by symptoms, although, of course, this is not reliable. Veran (11) had found that the shorter the duration of the disease, the higher the percentage of cures and the fewer the relapses.

One important difference in our figures is noted in comparative results in unilateral and bilateral cases. Thus 7 out of 62 unilateral cases are active at the present, as compared to 13 out of 54 bilateral cases. This indicates the importance of an early diagnosis and the institution of collapse therapy before the case has become bilateral. All contralateral lesions are potentially dangerous.

The end-results were superior in pneumothorax induced for patients without cavities. Only one is at present active out of 23 such cases. We could not demonstrate that cavity size played a part. There is no necessary relation between size of cavity and tissue destruction since physiological variations in size may be due to bronchial changes. The question of an early induction of pneumothorax for a lesion without cavity but with positive sputum is an important one to be considered. The outcome is favorable in our group but whether bed-rest would have given as good results with the noncavernous cases is uncertain. Barnes (12) found 40 per cent of noncavernous cases with positive sputa dead

in three years after conservative treatment. Pneumothorax is not innocuous, as Pinner, Leiner and Zavod (13) have shown by bronchospirometry that the reëxpanded lung though appearing intact may be functionally disabled.

The study of relapsed cases brings out several important points. It is impossible to forecast the outcome of any case until a long enough period of follow-up has been obtained. For instance, we note that most of our cases showed relapses more than one year after discontinuance. This is especially true in cases of homolateral breakdown where pneumothorax played a real part. It is interesting to note that only in one case has a breakdown occurred in the 26 cases which have been followed now for four years or longer after expansion. In other words, a breakdown will occur ordinarily from one year to three years. This suggests that a follow-up should be fairly intensive with periodic X-ray and sputum check, every three months, for at least a three-year period, and only after three years can one relax observation.

We do not feel that the existence of pneumothorax on one side had any particular effect on the contralateral lesion, but that the contralateral lesion pursued its evolution depending upon its character, whether productive or exudative.

The character of the collapse seems to us to be of prime importance in the outcome of the disease. Where the pneumothorax was perfect, that is, without adhesions (group 1) our figures show no relapses on the homolateral side, whereas 12 relapses occurred in groups 2 and 3. One should therefore try to obtain as perfect a collapse as possible, even if sputa are negative and no cavities are seen. No cases with perfect collapse showed reactivation in the homolateral lesion.

We feel that, if pneumothorax is not to fall into disrepute due to frequent reactivation, one should not remain satisfied with conversion as a criterium for good results but, rather, an anatomically perfect collapse should be obtained.

There has been considerable difference of opinion as to the method of reëxpansion. Dundee and others gradually prolonged the interval of pneumothorax until the lung had totally expanded. Our pneumothorax refills were stopped abruptly. This did not seem to predispose toward massive effusion of which we had 11 cases. Fluid usually accompanying pneumothorax was spread over the surface of the expanding lung and appeared larger than it actually was. None of our cases showed relapses on the pneumothorax side until at least one year after cessation. We

do not see any particular point in the method of gradually allowing the lung to expand, as most relapses will occur sometime after the lung has completely expanded. We did not observe any case that showed reopening of a cavity or recurrence of a lesion, immediately on expansion. Therefore, no lung required immediate recollapse.

This is important because very often as the lung reëxpands, many pseudo-cavity ring shadows are formed by local pleural thickening, areas of fibrosis, areas of emphysema and small, pocketed pneumothorax and hydropneumothorax. Consequently, although one naturally watches the lung carefully as it reëxpands, one cannot prognosticate the outcome by what one observes at this time. Rarely was it found necessary to withdraw any fluid which formed at the time of reëxpansion, since it did not seem to cause symptoms, although it did sometimes interfere with perfect visualization of the lung.

SUMMARY AND CONCLUSION

1. We have reported 117 cases of abandoned pneumothoraces, all of whom have had collapse therapy for at least two years.

2. These cases have been followed since discontinuance for an average period of four years.

3. Of these 117 cases, at present, one is dead, 79 apparently cured, 16 arrested and 21 active.

4. There were 12 homolateral and 17 contralateral relapses.

5. Contralateral disease has a definite deleterious effect on the outcome of reëxpanded pneumothorax cases so that cases of bilateral disease have a more serious prognosis than those of a unilateral disease.

6. The best results were observed in cases with at least four years of pneumothorax.

7. Abrupt cessation of refills and careful watching of the lung as it reëxpands is preferable to gradual reëxpansion of the lung.

8. Early pneumothorax in positive sputa cases is indicated regardless of the absence of cavity.

9. Best results are observed in cases with ideal collapse, that is, without adhesions to apex or costal wall. Therefore, early Jacobaeus operation should be considered in cases with adhesions, even though the sputa are negative.

10. Final outcome in reëxpanded pneumothorax cases cannot be ascertained until at least three years after reëxpansion.

11. Although ultimate results are not as favorable as immediate results

in pneumothorax, pneumothorax treatment seems preferable to conservative methods of treatment in positive sputum cases.

SUMARIO Y CONCLUSIONES

1. Estúdianse 117 casos de neumotórax abandonado, en todos los cuales la colapsoterapia duró por lo menos dos años.

2. Estos casos han sido seguidos desde que se abandonó el neumotórax, por un período medio de cuatro años.

3. De los 117, hoy día uno ha fallecido, 79 se encuentran aparentemente curados, 16 estacionados y 21 activos.

4. Hubo 12 recidivas homolaterales y 17 contralaterales.

5. La afección contralateral ejerce un efecto nocivo bien definido sobre el resultado obtenido en los casos de reexpansión del neumotórax, de modo que en los casos bilaterales el pronóstico es más grave que en los unilaterales.

6. Los mejores resultados fueron observados en los casos en que el neumotórax había durado por lo menos cuatro años.

7. El cese brusco de los rellenos y la cuidadosa vigilancia del pulmón a medida que se reexpande, son preferible, a la reexpansión gradual.

8. En los casos de esputo positivo, está indicado el neumotórax temprano, independiente de si hay o no cavernas.

9. Los mejores resultados corresponden a los casos de colapso ideal; es decir, sin adherencias al vértice o a la pared costal, por lo cual debe considerarse la ejecución de una operación de Jacobaeus temprana en todo caso de adehrencias, aunque el esputo sea negativo.

10. En los casos de reexpansión del neumotórax no puede averiguarse el resultado definitivo sino por lo menos hasta tres años después.

11. Aunque el resultado final no es tan favorable como el inmediato en el neumotórax, la colapsoterapia parece preferible a los métodos conservadores de tratamiento en los casos de esputo positivo.

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PROGNOSIS AND TREATMENT OF MINIMAL PULMONARY TUBERCULOSIS[1,2]

I. D. BOBROWITZ

LITERATURE

The treatment of minimal pulmonary tuberculosis is a problem of increasing importance. As public health measures to control tuberculosis and case-finding programs constantly progress and improve, the percentage of minimal cases found shows a steady rise.

A clear illustration of this is revealed in the examination of the statistics of the diagnostic clinics of the Department of Health of the City of New York for the past ten years (Edwards (1)). Between 1931 and 1936 inclusive, the average yearly percentage of minimal cases of pulmonary tuberculosis diagnosed in adults and children was 32.5 of the total number of cases. During the last four years (1937 to 1940, inclusive) this percentage has advanced to 48.2.

However, statistics for admissions to the tuberculosis hospitals serving New York City (Drolet (2)) have disclosed that during the past four years (1937 to 1940, inclusive) the percentage of minimal cases has varied but little and has averaged 10.7.

Likewise Frankel (3), reporting on first admissions to the State and County sanatoria of New Jersey, demonstrated that between 1929 and 1939 there has been a gradual drop in the proportion of minimal patients from 18.7 to 10.4 per cent. Apparently, then, a great number of early cases of tuberculosis receive clinic or home care.

The future will show, no doubt, a great increase in the diagnosis of tuberculosis in the early stages. The routine X-ray examination of hundreds of thousands of young people in the military forces alone will yield a considerable number of new cases. It is almost safe to predict that in time our enlarged and more effective public health programs will eventually realize a reversal of the present ratio of 85 to 90 per cent

[1] From the Municipal Sanatorium, Otisville, New York (one of the institutions of the Department of Hospitals of the City of New York).

[2] Presented at a meeting of the Clinical Society of the Otisville Sanatorium, in New York City, April 22, 1941.

admissions to tuberculosis hospitals of moderately and far advanced cases, to a proportion of 85 per cent, or more, in the minimal stage. Predictions have been made concerning the eradication of tuberculosis by 1960, but before that occurs the disease must be found and treated early.

There are no uniform ideas concerning the prognosis and treatment of minimal tuberculosis. Both conservative and aggressive methods of treatment have been advocated.

Moore (4) recommends pneumothorax for minimal tuberculosis without waiting. He claims that, if cases are observed for progression, pneumothorax will be less successful, as few small lesions are healed in a short time by bed-rest and, with the formation of cavities, adhesions will surely be present. Rather than wait for possible progression, every lesion, no matter how small, should be treated as progressive. Other complications, such as fluid and bronchopleural fistula, will also be less frequent. Moreover, because of little destruction of lung tissue, pneumothorax will be necessary for only a few months or a year at most. He believes the chances are best with this therapy for a perfectly functioning lung after reëxpansion, and economically the patient has the great advantage of requiring less time for treatment and returning early to former activities. Moore quotes no statistics but claims from fifteen years observation that results are better with pneumothorax in minimal cases than if one waits till the lesion progresses to a moderately or far advanced stage.

The use of early collapse measures is strongly urged by Thomas and Davis (5) to obtain, in a vast majority of cases, a rapid cure. They state that thus will be avoided the morbidity and mortality that is associated with advanced lesions. They "see nothing rational in waiting until cavernous or wide spread lesions appear, with their complications of adhesions and pyogenic infections. Such complications at once make almost certain bronchiectatic and atelectatic complications, as well as certain sepsis with its further disabling effects . . . continued morbidity and prevention of complete economic restoration."

The institution of pneumothorax as soon as possible after diagnosis is made, even in minimal cases, is the suggestion of Chadwick and Evarts (6).

Turner and Collins (7) conclude from a study of 139 minimal cases, of which 75 had sanatorium treatment, 24 sanatorium treatment and phrenic crush or exairesis, and 40 the usual sanatorium treatment and pneumothorax, that conservative therapy and waiting in minimal cases for progression is dangerous and costly and advocate immediate induc-

tion of artificial pneumothorax in definitely diagnosed minimal cases. They favor pneumothorax over phrenic operations and describe a high percentage of satisfactory collapses, infrequent complications, prompt sputum conversions and decreased hospital stay and disability.

In discussing the choice of procedure in collapse therapy, O'Brien (8) has stated that "our best opportunity to control the disease exists in the treatment of early minimal lesions. We cannot tell when we first see a patient what course the disease will take and many even though hospitalized, if left to bed-rest alone, will progress rapidly into far advanced disease."

Analyzing 1,124 patients who had collapse therapy of some kind, Leslie and Anderson (9) conclude that "With the exception of the following three categories of patients, we believe that practically all patients admitted to a sanatorium with the adult type of active pulmonary tuberculosis, should have collapse therapy: 1. Terminal Cases. 2. Those whose lesions are questionably active (the majority of such patients actually do not require hospitalization). 3. Those who refuse collapse therapy or who leave the sanatorium for various reasons before collapse therapy is instituted."

The utilization of artificial pneumothorax only in progressive minimal pulmonary tuberculosis has been advocated by Myers and Levine (10). In consideration of minimal lesions of the reinfection type, they maintain that "Those which are not increasing in extent, are not breaking down, are not discharging tubercle bacilli, etc., do not need hospitalization or any drastic form of treatment. Well regulated living suffices provided they are kept under close observation. But these minimal lesions which are progressive, even though they are causing no symptoms, no abnormal signs and tubercle bacilli cannot be demonstrated in the sputum, should be treated drastically. Strict bed-rest fails sufficiently often in such cases as to make us feel that this treatment alone is not dependable."

They reported 52 cases and of these 4 died without pneumothorax responsible, 4 showed spreads and 42 are already working or ready to work and only 3 cases had adhesions that interfered with the collapse.

The use of artificial pneumothorax in minimal tuberculosis, only when a preliminary period of rest of one to three or four months does not show favorable progress or improvement, or if a positive sputum persists, is recommended by Friel (11), Hegner (12) and Matson (13).

For the treatment of early pulmonary tuberculosis, Amberson (14) advises a period of strict bed-rest. Pneumothorax or phrenic crush may

be required if the patients do not show steady favorable progress with bed-rest alone. "Since these measures occasionally are attended by hazards, some great and some small, there should be a specific and positive reason for using them. They are not necessary for the satisfactory clinical cure of most early infiltrates, and with the exception stated, there is no convincing evidence that they shorten the desired time of treatment. Patients treated promptly and with bed-rest at the start have recovered without progression of the lesion in about 90 per cent of the instances. In most of the others, advancement or relapse, if any, has been promptly detected and usually controlled by artificial pneumothorax. Considering the permanence of recovery, preservation of pulmonary function and working ability after treatment, the experience has been much superior to any other plan attempted."

Schoenheit (15) also emphasizes that the patient should have an opportunity to improve on rest. He does not believe that all pulmonary tuberculosis in time becomes a surgical disease. Because of the dangers and complications of pneumothorax and other collapse measures, they should be used only after failure of rest to improve the patient.

Alexander (16) has noted that collapse therapy is only occasionally necessary, as minimal tuberculosis is usually controlled by rest. In the few cases where this result does not obtain, paralysis of the diaphragm will control the great majority. "There are a few remaining cases that are progressive from the first observation and continue so in spite of bed-rest and phrenic paralysis. In these very few, pneumothorax is not only justifiable but mandatory."

OBSERVATIONS

In order to evaluate the methods of treatment of minimal pulmonary tuberculosis and determine the prognosis of this type of lesion, 190 patients with minimal infiltrations, discharged from the Municipal Sanatorium, Otisville, New York, in 1934 and 1935, were analyzed. All of these cases were again studied in July, 1940 and comparison made between their condition on discharge and their last follow-up examination. This was accomplished by review of the X-ray films and charts on discharge and those of the Board of Health Clinic, hospital or private doctor that had furnished treatment for the patients during the follow-up period. These data were supplemented by questionnaires submitted to all the patients.

The Department of Health X-ray films and records were examined

in collaboration with Dr. A. Robins of the New York City Health Department, who very kindly provided this valuable coöperation and help.

Of the 190 patients, 120, or 63.1 per cent, were discharged on the recommendation of the Visiting Physicians of the Medical Board; 62 patients, or 32.6 per cent, left the institution against the advice of the medical staff; 2 cases, or 1.0 per cent, were disciplinary discharges and 6, or 3.1 per cent, were transfers to other hospitals.

The entire group consisted of 86 males (45.2 per cent) and 104 females (54.7 per cent), of whom 174, or 91.5 per cent, were white and 16, or 8.4 per cent, were black. As regards the marital status of the patients, 71, or 37.3 per cent, were single; 104, or 54.7 per cent, were married; 9, or 4.7 per cent, were separated or divorced; and 6, or 3.1 per cent, were widowed.

The age of the patients is shown in table 1.

TABLE 1

Age of patients on admission

AGE IN YEARS	NUMBER OF PATIENTS	PERCENTAGE
15–19	19	10.0
20–29	76	40.0
30–39	70	36.8
40–49	19	10.0
50–59	6	3.1

The age factor of the patients admitted here has varied but little during many years, and the incidence of 40 per cent between the ages of twenty and twenty-nine, and over 75 per cent between twenty and thirty-nine years, only emphasizes again the tragedy and importance of tuberculosis with its preponderance during the most useful and productive periods of life.

These 190 patients were hospitalized for variable periods of time as outlined in table 2.

The 79 cases, or 41.5 per cent of the discharges with three months or less of hospital care and the 34 cases, or 17.9 per cent with four to five months hospitalization might indicate a period of hospital observation and treatment that was not sufficient. On the other hand, the 87.3 per cent discharged with nine months or less of care would not signify that rest treatment, *per se*, had unduly prolonged the period of hospitalization. However, consideration must be given to the treatment or hospitaliza-

tion that preceded arrival in the Sanatorium, the physical condition of the patient, sputa, stability of the X-ray lesion and the type and extent of pulmonary involvement, before proper determination of an adequate hospital stay can be made.

The 77, or 40.5 per cent of the patients with six months or more of hospitalization, do not include entirely all those patients with a suitable

TABLE 2

TIME HOSPITALIZED	NUMBER OF PATIENTS	PERCENTAGE
months		
0–1	33	17.3
2–3	46	24.2
4–5	34	17.9
6–7	30	15.8
8–9	23	12.1
10–11	13	6.8
12–15	7	3.7
16–20	2	1.0
21–25	1	.5
3 years	1	.5

TABLE 3

Time of discharge

During 1934:	January to March	13	
	April to June	20	17.4%
	July to September	23	
	October to December	13	18.9%
	Total	69	or 36.3%
During 1935:	January to March	21	
	April to June	19	21.1%
	July to September	34	
	October to December	47	42.6%
	Total	121	or 63.7%

sanatorium stay, as many with shorter periods of care were arrested. The patient hospitalized for three years was an ex-patient employee.

The patients were discharged during the periods of 1934 and 1935 shown in table 3.

There is a progressive increase in the number of discharges from early 1934 to the end of 1935, with percentages of 17.4, 18.9, 21.1 and 42.6 for each six months' period from January, 1934 to December, 1935.

In the discussion of the other details of these cases, the number of patients included in the several tables differ as the information obtained from the doctor, clinic, hospital or patient varied in completeness.

TABLE 4

Type and extent of pathology

TYPE	NUMBER OF PATIENTS	RESOLUTION
A. Unilateral:		
1. Small localized area of fibrosis	42	12
2. Small localized area of infiltration	42	16
3. Scattered areas of infiltration in upper lobe	15	2
4. Scattered areas of fibrosis in upper lobe	21	3
5. Fibrocalcific area	3	
6. Infiltration with partial small pneumothorax	1	
Totals	124	33
B. Bilateral:		
1. Fibrosis of upper lobes	16	3
2. Infiltration both upper lobes	19	6
3. Infiltration one upper and fibrocalcific spots in other upper lobe	3	1
4. Bilateral fibrocalcific spots	3	
5. Fibrosis in one upper lobe and infiltration in other apex	3	
Totals	44	10
C. Thick Pleura:		
1. After absorption of fluid and with very small unilateral infiltrate	5	1
2. After absorption of fluid and with very small contralateral infiltrate	1	1
3. Thickened pleura, unilateral	3	
Totals	9	2
D. Increased Lung Markings:		
1. After practically complete resolution of small infiltrate	3	3
2. During entire stay without definite parenchymal infiltration	8	
3. With enlargement of the hilar node area	2	
Totals	13	3
Grand Total	190	48 or 25.2%

Of the 190 patients, 184 were checked on discharge by X-ray films and in 6 cases X-ray reports were used.

Table 4 indicates the type and extent of pathology and the changes that occurred during the sanatorium period of observation. Only those cases that could be considered minimal according to the classification of

the National Tuberculosis Association were included. No distinction was made between early cases and minimal ones. All of the patients had a minimal involvement during their entire period of sanatorium observation.

In tabulating the findings in table 4 fibrosis indicates X-ray lesions where the productive elements are prevalent and most of the radiographic shadows appear hard and well defined with a clear outline. Infiltrates refer to lesions where the exudative element predominates with soft, hazy areas. Resolution signifies an absorption of the lesion to a greater or lesser extent.

In recapitulation, 124 patients, or 65.3 per cent, had unilateral lesions; 44, or 23.1 per cent, bilateral lesions; 9, or 4.7 per cent, thick pleura; and 13, or 6.8 per cent, an increase in lung markings.

TABLE 5

Sputum findings

NEGATIVE GROUP		POSITIVE GROUP	
Sputum always negative	100	Alternately negative and positive	2
Sputum always negative including gastrics and cultures	54	Always positive	3
Positive once on admission, then negative	13	Usually positive	2
Positive at first then negative	10	Negative first, then positive	2
		Sputum always negative and negative gastrics, with exception of one positive gastric	4
Total	177	Total	13

Thus 33, or 26.6 per cent of the unilateral cases, or 17.3 per cent of the entire series of 190 cases showed resolution, whereas 10, or 22.7 per cent of the bilateral cases, or 5.2 per cent of the entire series showed some absorption. The value of observation of fibrotic lesions is indicated by the number that showed gradual degrees of resolution.

Two of the cases with thick pleura and 3 of the group with increased lung markings had resolution. Including these latter two groups, there was a total of 48 patients with evidence of clearing to some degree of the X-ray lesions, a percentage of 25.2 of the 190 cases. This is evidence of the value of bed-rest.

One of the most important criteria of treatment and prognosis in tuberculosis is the presence or absence of tubercle bacilli in the lung expectoration. The condition of the sputum of these patients is shown in table 5.

In recapitulation, 177, or 93.1 per cent of the patients are in the negative group and 13, or 6.8 per cent, are in the positive group. However, in 1934 not many gastrics and cultures were done.

The good general condition of these patients is indicated by the gain in weight of 151, or 79.4 per cent, during their hospital stay, with only 26, or 13.7 per cent, showing a loss of weight, and 11, or 5.8 per cent, with no change in weight. Two cases, or 1 per cent, had no complete records about weight changes.

In the majority of the patients, 160 or 84.2 per cent, there were no complications. There were single cases of healed tuberculosis of the larynx, and questionable tuberculous peritonitis, and one patient with tuberculous peritonitis and glandular tuberculosis, 5 patients with pleurisy, 6 with an enlarged thyroid, 3 with pregnancy, 3 cases of bilateral salpingitis and endocervicitis and 10 cases with general medical and gynecological and surgical ailments.

At the time of discharge, 154 patients, or 81 per cent, had no symptoms. Expectoration was complained of by 15 patients, or 7.9 per cent, and cough and expectoration by 17, or 8.9 per cent. One case had cough and slight dyspnoea and chest pain. There were single cases with complaints of digestive disturbances, loss of weight and fever and convulsions.

All the patients, except 3, had routine treatment, that is, sanatorium observation, bed-rest and symptomatic care, with gradual increase in physical activities and occupational therapy when the physical condition improved. Of the 3 exceptions, 2 had pneumothorax attempted and one had pneumothorax. Those patients with gynecological or surgical complications had special treatments.

The activities of the patients were classified according to their physical condition, need for bed-rest and ability to partake of ambulatory functions and occupational therapy. These activity groups are as follows:

Activity 0—Absolute bed-rest in the Infirmaries
Activity I—Patients on bed-rest with bathroom privilege
Activity II—Patients allowed to have meals in the dining room on wards, the remainder of the time at rest
Activity III to VI—Patients in ambulatory pavilions—may attend church and movies and may perform various ward duties
Activity IV to VI—Patients on occupational therapy, with gradual increase in therapy till on two or three hours, or more, morning or afternoon, at time of discharge

On discharge the patients' activities were classified as in table 6. Although this table is not complete because of 41 cases whose activities

are unknown, still it is clearly evident that a good physical condition of the patients must obtain to permit the great majority of them, 91.3 per cent, to be ambulatory, with 109, or 73.1 per cent, engaged in some form of occupational therapy. This therapy covered a multitude of forms and included many arts and crafts, such as leather, metal and needle work, painting, reed weaving, wood carving, book binding, embroidery, making of hooked rugs, table-loom weaving, and wood-block

TABLE 6

Activity on discharge

	NUMBER OF PATIENTS		PERCENTAGE
Activity I	6		
Activity II	7	13	8.7% of 149 known cases
Activity III	27		
Activity IV	34		
Activity V	38		
Activity VI	37	136	91.3% of 149 known cases
Total			149
Activity not known			41

TABLE 7

Condition on discharge

Arrested	60	
Apparently arrested	48	108 or 58.4%
Improved	12	
Inactive	3	
Improved inactive	35	
Quiescent	6	56 or 30.2%
Total		164 or 88.6%
Improved active	10	
Unimproved	11	21 or 11.3%
Total		185 known cases
Unknown		5

printing. The patients also assisted in the various offices of the Sanatorium, doing stenography, clerical work and typewriting, and engaged in other miscellaneous occupations, such as laboratory technician, gardner, librarian, messenger and ward helper.

The classification of the condition of the patients on discharge followed closely the requirements described by the National Tuberculosis Association (table 7).

The value of the sanatorium care is clearly illustrated: 164, or 88.6 per cent of the patients showed definite benefit from the treatment and were not active at the time of discharge. Even the 10 active cases had shown some improvement; 58.4 per cent of the patients were apparently arrested or arrested and many of the patients grouped as apparently arrested had negative sputum for more than three consecutive months. This creditable achievement includes 62 patients, or 32.6 per cent, who left against advice. Otherwise the percentage of arrests would be greater as no patient is routinely discharged by the Medical Board until this status is reached. The therapeutic regimen that produces such results is definitely highly satisfactory, but the value of these results can be properly interpreted, however, only with a sufficiently long follow-up period.

TABLE 8

Follow-up care

Board of Health clinics	78	
Hospital clinics	26	
Private doctors	8	
Hospitals	6	
Combinations of above agencies	55	
Readmissions	3	176
Unknown		14
Total		190

Table 8 outlines how these patients received observation and treatment after their discharge.

Practically all the patients in the Sanatorium are charity cases and consequently they almost all return to hospitals or Board of Health clinics. It is interesting to note that 176, or 92.6 per cent of the patients received known care after discharge. This high figure makes the follow-up study more significant. Besides the 3 patients directly readmitted to the Municipal Sanatorium, 8 others were eventually readmitted.

The value of all follow-up studies is directly related to the time interval that has elapsed between the contacts with the patient. This is particularly important in tuberculosis as no proper interpretation of treatment can be made without observation for at least three to five years, or more.

The time interval between the patient's discharge and the last follow-up contact is listed in table 9.

Thus, 125 patients, or 71 per cent of the above 176, were followed up for three years or more, with 68, or 38.6 per cent, for five years or more, and 51, or 28.9 per cent, were seen for less than three years.

Many of the patients had their follow-up terminated shortly after discharge because of their classification as Arrested or "As no longer in need of observation." Other patients stopped their check-up visits voluntarily.

In the follow-up contact with the various agencies providing care for the patients, in 129 instances X-ray films were available. Of the 176 patients contacted, this represents 73.3 per cent, or 67.9 per cent of the original 190 cases.

The examination of these films, and comparison with the final discharge films in 1934 and 1935, revealed the data given in table 10.

Of the 129 patients with available comparative X-ray studies, 103, or 79.8 per cent, were unchanged or improved; 26 patients showed pro-

TABLE 9

Time between discharge and last follow-up examination

	YEARS													TOTAL
	½	1	1½	2	2½	3	3½	4	4½	5	5½	6	6½	
Number of patients	17	8	5	4	17	7	10	6	34	19	22	15	12	176

gression or needed collapse therapy because of spread or progression of the lesion, a percentage of 20.2. Of these 26, 5 patients became moderately advanced, 3 far advanced and 5 progressed, but with pneumothorax present the extent was not accurately determined.

The proportion of good to poor results is therefore four to one. A certain number of the cases that have progressed will become arrested, no doubt, with continued rest. If active therapy had been instituted for all minimal cases, unnecessary collapse therapy would have been used for at least 80 per cent of the patients.

These studies reveal that unilateral cases do much better than bilateral ones. Patients with X-ray improvement show, with decreasing frequency, resolution, increase in fibrosis or complete clearing of the lesions.

A review of the case records of 23 other patients, besides the 129 with X-ray films, yielded additional information and provided a group of 152 patients for study.

Among this group of 152 patients, tuberculous complications were found in 14 cases, and general medical and surgical conditions in 14 others. The tuberculous complications included 7 patients with effusion, 6 during the course of pneumothorax therapy; 2 patients with tuber-

TABLE 10

Follow-up X-ray changes

Group A: Patients with no change		
1. Unilateral cases	44	
2. Bilateral cases	7	
Group B: Patients with improvement of lesion		
1. Resolution of infiltration, unilateral	21	
Resolution of infiltration, bilateral	3	
2. Increase in fibrosis, unilateral	17	
3. Complete clearing of lesions		
a. Small localized area	6	
b. Unilateral areas	4	
4. Absorption of unilateral effusion	1	
Total	103	or 79.8%
Group C: Patients with progression of lesion		
1. Unilateral progression	7	
2. Bilateral progression		
a. Increase of bilateral infiltration	3	
b. Cavitation on one side and increase in nodular infiltration, bilaterally	4	
c. Cavitations on both sides	2	
Group D: Patients who received collapse therapy		
1. Pneumothorax		
a. Unilateral	5	
b. Reëxpanded	3	
2. Thoracoplasty	1	
Group E: Patients with improvement and progression		
1. Resolution in one area of infiltration with spread on same side	1	
Total	26	or 20.2%

culous enterocolitis, one associated with amyloid disease and the other with a spontaneous pneumothorax; one case of tuberculosis of the larynx; 2 patients with disseminated tuberculosis; one with a tuberculous lobar pneumonia; and lastly, one case of tuberculosis of the spine with paravertebral abscess formation and spastic paraplegia.

Besides routine care, surgical treatment and collapse therapy was instituted in the following manner:

Unilateral pneumothorax	10
(Two of these patients had Jacobaeus operations and one had a thoracoscopy)	
Bilateral pneumothorax	1
Phrenic operations	2
Extrapleural pneumothorax	1
Thoracoplasty	1
Intestinal resection	1

The intestinal resection of the terminal ileum and ascending colon was done for ileocaecal tuberculosis.

Of the 2 patients with phrenic operations, one was arrested on discharge and the other improved, but later showed progression of the lesion and a positive sputum.

The patient with extrapleural pneumothorax was formerly discharged as apparently arrested.

Of the 10 pneumothorax cases, 6 were formerly discharged by the Medical Board as arrested; 2 of these patients were in the group who were transferred from the Sanatorium, one for pregnancy with a progressive lesion and positive sputum, and one for bronchoscopy with a positive sputum. Two of the cases had previously signed out against advice; both had progressive lesions and positive sputa.

The bilateral pneumothorax was done for a patient who had been discharged for disciplinary reasons and, though his condition was improved, the lesion progressed.

The thoracoplasty was performed on a patient who had signed out after one month in the Sanatorium and left in an improved condition.

Even after long periods of observation only 15 patients (less than 10 per cent) required collapse therapy. There is a possibility, also, that the 4 cases that were discharged against advice or for disciplinary reasons might not have come to collapse therapy if proper hospitalization had been continued. Very significantly, only 7 patients previously discharged as arrested and one as apparently arrested, by the Medical Board, ultimately received collapse treatment.

An indication of the follow-up status of these patients is also shown by the number that required hospitalization after discharge. Six patients were admitted to general hospitals for medical, surgical and gynecological conditions, and 3 were admitted to mental hospitals for psychoses. Hospitalization in tuberculosis institutions was required in 7 cases for an

increase of tuberculosis symptoms, for 16 patients because of progression of pulmonary tuberculosis and for 4 others with extrapulmonary tuberculous complications. These 27 tuberculosis admissions represent a percentage of 17.7 of the 152 patients with follow-up records.

The sputum reports during the former period of hospitalization of these patients were compared with the sputum findings during their entire follow-up period. These results could be grouped in four classifications—those that remained unchanged, changes from positive to negative, or negative to positive, and those that were unknown (table 11).

Of the 156 known cases, 96, or 61.5 per cent, remained negative and 23, or 14.7 per cent, were converted from positive to negative, a total of 119 cases, or 76.3 per cent, that were negative on follow-up. Only 8 patients remained positive and with the 29 cases that turned positive after a former negative sputum, this percentage of positive sputa becomes 23.7.

TABLE 11

Comparison of sputum findings

1. Unchanged		
a. Negative	96	
b. Positive	8	104
2. Changes from positive to negative		23
3. Changes from negative to positive		29
Total		156
4. Unknown		34

However, many of the positive cases were only positive once during the follow-up period and of the 34 unknown sputa cases there were many who had conditions compatible with a negative sputum. If these cases were considered in the negative group our percentage of negative patients would be over 80.

The classification of the physical condition of all the patients, including those hospitalized, is tabulated in table 12.

The definitely good results include 137 patients, or 86.7 per cent of the 158 known contacts. The poor results, 21 cases, represent 13.3 per cent. Although it is not known whether these results were checked by all the agencies in conformity with the National Tuberculosis Association classification, it is still evident that the patients with a poor end-result, following observation and care, form a very small minority, even including all the complications, hospitalization and therapy required. It demon-

strates emphatically the value of the conservative method of care recommended for the patients early in treatment.

The 11 deaths were attributed to the following causes: Extensive pulmonary tuberculosis was the diagnosis in 7 patients—one of these was complicated by miliary tuberculosis, tuberculous enterocolitis and peritonitis, and another had intestinal tuberculosis and amyloidosis. One patient had pulmonary tuberculosis, but the principal lesion was tuberculosis of the dorsal spine with paravertebral abscess formation and spastic paraplegia. One case was diagnosed as tuberculous lobar pneumonia. Another patient had tuberculous mesenteric adenitis, pleurisy, a ventral hernia and multiple abscesses. Finally, one patient had a nontuberculosis death, with a diagnosis of cerebral haemorrhage, enlarged heart, hypertension, syphilitic aortic insufficiency and stenosis.

TABLE 12

Physical condition on follow-up

Excellent or apparently cured	15	
Arrested	95	
Good	16	
Discharged from clinic	3	
No tuberculosis	6	
Improved	1	
Inactive	1	137—86.7%
Poor	5	
Guarded	5	
Died	11	21—13.3%
Total		158
Unknown		32

The good prognosis of this entire group is demonstrated by the death of 11 of the 176 patients contacted, a mortality rate of 6.2 per cent.

From the information obtained it could not be concluded which of these deaths were attributable to failure to treat the minimal tuberculosis during former hospitalization, or those due to uncontrollable complications, or the number to be considered avoidable because of improper conduct by the patients, economic reasons or inadequate medical follow-up care.

COMMENT

We believe these studies, which entail an analysis and follow-up of 190 cases of minimal pulmonary tuberculosis discharged from the Municipal

Sanatorium in 1934 and 1935, indicate that early tuberculosis has a definitely good prognosis and conservative measures represent the logical method of treatment. The status of these patients after their hospitalization, which consisted of routine sanatorium care, showed that 25 per cent had evidence of resolution in some degree of their X-ray lesions, 93 per cent had a negative sputum, 79 per cent gained in weight, 81 per cent were without symptoms, 91 per cent had become ambulatory, 73 per cent had participated in some form of occupational therapy, 89 per cent were inactive; and of these, 58 per cent were classified as apparently arrested or arrested.

These results are extremely gratifying and satisfactory. No other method of treatment of tuberculosis offers more beneficial results with the promise of fewer difficulties, dangers and complications than those associated with bed-rest.

The proponents of aggressive treatment of early pulmonary tuberculosis advocate collapse therapy for minimal lesions principally because they feel it is dangerous to wait, as delay produces the probability of progression with cavitation, a lengthened hospital stay, more frequent complications of collapse measures and greater morbidity and mortality.

Our follow-up studies, with 93 per cent contacted after discharge and 71 per cent of the patients seen for three years or more, should denote whether the conservative measures adopted for the patients in the Sanatorium had dire results.

X-ray follow-up showed 80 per cent of the patients unchanged or improved, while 20 per cent progressed in some degree and only half of these beyond a minimal stage; 76 per cent had a negative sputum. Fourteen patients (less than 10 per cent) had tuberculous complications and 18 per cent were hospitalized because of progression of the disease or complications and 6 per cent are dead. Only 15 patients required collapse therapy and of these only 7 were previously discharged as arrested and one apparently arrested, by the Medical Board. Eighty-seven per cent of the group, including all those that required treatment, were considered to be in a good or arrested condition and only 13 per cent in a poor state.

Thus, every method of appraisal of activity and progress or arrest of tuberculosis has definitely shown that 75 to 80 per cent of our group was unquestionably in a satisfactory status. It is doubtful if a pneumothorax group, followed in a similar manner, would have shown as good

or better results. It would not have been logical or proper to institute collapse therapy with all its complications and dangers in a group of patients where several years of follow-up had shown that 80 per cent had controlled their tuberculosis and remained well without it, and less than 10 per cent had actually required collapse treatment.

True, occasionally a minimal case will progress and sometimes with rapid appearance of a caseous tuberculous pneumonia and cavitation. Tuberculous lesions, however, also progress even after phrenic operations or under pneumothorax therapy.

There should be no unnecessary delay experienced for those patients that require collapse measures. Under proper observation and expert medical guidance the treatment can be started in time. It should be emphasized that conservative therapy is not safe unless this proper observation can be obtained.

Waiting in minimal cases doesn't mean waiting for progression. The above statistics demonstrate that very infrequently do they advance to a moderately or far advanced stage. While the patient is being observed resolution usually occurs, or the lesion becomes stable or fibrotic.

Conservative therapy doesn't imply an increased hospital stay. Our experience has indicated that patients with collapse therapy remain in the institution longer than those on routine care. This results from the need of an observation period to precede the initiation of the pneumothorax, the addition of intrapleural pneumonolyses or other measures to aid the collapse, and the continuation of hospitalization until the collapse is satisfactory and the patient in condition to be handled easily in an outside clinic. This does not pertain to those hospitals where a direct policy of ambulatory pneumothorax is used and patients are discharged shortly after the initial pneumothorax.

The presence of so many cases with fibrotic lesions doesn't detract from the value of the conservative care rendered, for these lesions at one time were exudative in nature and the fibrosis resulted from rest.

The admissions to tuberculosis institutions and the deaths that occurred during the follow-up period would not have been avoided in each instance if collapse therapy had been instituted during their hospitalization, although a few may have been prevented. Many of the hospitalized cases have become inactive with a good prognosis. Complications and deaths also result from uncontrollable pathological sequences of the tuberculous process, others occur because of the failure of the patients

to conduct themselves properly and avoid circumstances that are conducive to the relapse of the disease, and additional responsible factors include economic insufficiency, and inadequate and incomplete follow-up care. Consider the end-results of pneumothorax therapy and there is no indication that the routine use of pneumothorax for these patients would have resulted in fewer complications or deaths during a follow-up period that extended for over six years.

Each case of minimal pulmonary tuberculosis is an individual problem. The mere presence of tuberculous infiltration is not in itself a sufficient indication for routine collapse therapy. Early tuberculosis is associated with an excellent prognosis. Every case of minimal tuberculosis, therefore, deserves a period of bed-rest. If the lesion continues to resolve, the sputum is negative and the general condition of the patient is good, conservative measures should be continued. If progression should occur in spite of bed-rest, collapse therapy is indicated without waiting, even if bed-rest has been used for only a few weeks. If the sputum remains negative, in spite of a progressive lesion, immediate collapse is deserved as the sputum does not become positive until lung destruction has occurred. A lesion that forms a cavity or is associated with a persistent positive sputum should be collapsed. Bleeding may need aggressive therapy. A stationary pulmonary process should receive conservative rather than radical therapy.

The adolescent group does not, because of age itself, demand collapse measures for early lesions. It has been emphasized that the adolescent patients have a poorer prognosis than older ones, and they especially require close observation, but there should be a specific reason in the behavior of the lesion to require collapse therapy, and not the presence of the tuberculosis alone.

To reduce the number of cases that progress after discharge or require collapse measures, patients should be hospitalized until their X-ray lesions are absolutely stable for at least six months. The National Tuberculosis Association requires, for the classification of the patient as arrested, that the X-ray findings for six months should be compatible with a stationary or retrogressive lesion. However, resolution or retrogression signifies an unstable lesion and treatment should be continued until the X-rays show no changes and definite stability has been present during a period of at least six months. These requirements, added to the other National Tuberculosis Association criteria of arrest, would safely indicate the classification of the tuberculous process as arrested.

CONCLUSIONS

1. One hundred and ninety patients with minimal pulmonary tuberculosis, discharged from the Municipal Sanatorium in 1934 and 1935, were analyzed and followed up for periods up to six and a half years, with 93 per cent contacted after discharge and 71 per cent followed up for three years or more.

2. The study indicates that routine collapse therapy of minimal pulmonary tuberculosis is not justified. Conservative therapy is the treatment of choice. From 75 to 80 per cent of the cases resolve or fibrose and become stable with bed-rest and remain well. Collapse therapy should be instituted only when specially indicated.

CONCLUSIONES

1. Ciento noventa y cinco enfermos con tuberculosis pulmonar mínima, dados de alta del Sanatorio Municipal de Otisville en 1934 y 1935, fueron analizados y seguidos por períodos hasta de seis años y medio, interrogándose a 93 por ciento después del alta, y siguiéndose a 71 por ciento por tres años o más.

2. El estudio indica que la colapsoterapia sistemática no está justificada en la tuberculosis pulmonar mínima, siendo el proceder de elección la terapéutica conservadora. De 75 a 80 por ciento de los casos se resuelven o fibrosan y estabilizan por medio del encamamiento, y continúan bien. En estos casos la colapsoterapia sólo debe ser instituída cuando está especialmente indicada.

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A SURVEY OF PERSONS EXPOSED TO TUBERCULOSIS IN THE HOUSEHOLD[1,2]

The Necessity for Prolonged Observation of Contacts

HENRY BEEUWKES, RICHARD G. HAHN AND PERSIS PUTNAM

Investigations were carried out in Philadelphia (1–3), Lee County, Alabama, and Jamaica, B.W.I. (4) between 1923 and 1938 which demonstrated the spread of tuberculosis among persons in families exposed to an individual with manifest disease in the household. During 1933 to 1938 a similar program was developed at the New York Hospital and Cornell University Medical College with the coöperation of the Department of Health, Bureau of Tuberculosis, of New York City. The purpose was to see whether events following exposure to manifest tuberculosis in New York households were similar to those observed elsewhere.

Shortly after the initiation of the program the pulmonary clinic at the New York Hospital became a voluntary city clinic serving a small district adjacent to the hospital. Later the district was enlarged, with its limits at Seventy-ninth Street on the north and Thirty-fourth Street on the south, with Fifth Avenue and the East River forming the western and eastern boundaries. The population was approximately 165,000. This area formed a part of what is now the Kips Bay-Yorkville Health District. Well-to-do and wealthy persons lived in the western third and along the middle eastern boundary; but the remainder of the district contained poorer families, many of whom were on relief, and these furnished the families under observation in the clinic. The population of the district was almost exclusively of the white race, and practically all the younger persons were native born. With the exception of the southeastern section of the district there were no typical, overcrowded tenement areas, such as are present in the lower eastern and western areas of Manhattan or in Harlem where the population is almost entirely Negro.

The mortality rate for tuberculosis in this district has varied from approximately 56.1 to 40.1 per hundred thousand from 1935 to 1939.

[1] From the Pulmonary Clinic of the New York Hospital, New York City.

[2] The studies and observations on which this paper is based were aided by a grant from the International Health Division of The Rockefeller Foundation.

CLINIC PROCEDURE

Persons suffering from manifest (clinical) tuberculosis and individuals who had been or still were exposed to the disease in the household were interviewed at the clinic and their histories and physical examinations were recorded.[3] A single anteroposterior roentgenogram of the chest was made, and additional roentgenographic examinations were carried out at the same time or later, if advisable. Sputum examinations were made. For these, three-day specimens were concentrated and a smear was made and stained. This method became the routine procedure, replacing the previous direct examination of single specimens collected on several occasions. In special instances guinea pigs were inoculated with samples of sputum and quite frequently with specimens obtained by gastric lavage. Cultures of specimens were made very infrequently.

All tuberculin tests were made by the intracutaneous injection of a specified amount of commercial Old Tuberculin,[4] and the result was noted forty-eight hours later. At the initial test 0.01 mg. was injected, and if this amount failed to elicit any reaction 1.0 mg. was given.[5] The intensity of the reaction was recorded as follows: One plus (+), redness with slight but definite oedema of 1 mm. or less over an area of about 10 mm. in diameter; two plus (++), well defined oedema, raised more than 1 mm. over an area about 15 mm. across; three plus (+++), extensive oedema raised 2 mm. or more over 15 mm. across; and four plus (++++), extensive oedema with necrosis. Oedema was considered more important than redness. Absence of oedema, with or without redness, was interpreted as no reaction.

The length of the interval between examinations of persons suffering from tuberculosis or with a latent (asymptomatic) lesion depended on many factors. The general policy was to secure hospital or sanatorium care as soon as possible for all persons with lesions obviously or potentially dangerous either to themselves or to others. Persons exposed to manifest tuberculosis (contacts) whose first examination did not reveal latent or manifest disease were reëxamined at six-months or yearly intervals, depending on their age, the amount of exposure and their general condition. Many contacts returned to the clinic more frequently and all of them were urged to return if they developed any symptoms of ill health during the interval between their regular appointments, and not to disregard any persistent cough that seemed to be associated with a cold.

[3] The staff consisted of the Chief of the Pulmonary Clinic of the New York Hospital, two full-time physicians from The Rockefeller Foundation, two full-time visiting nurses, a clinic nurse, and four to six physicians appointed to the Clinic by the Medical Department of the New York Hospital.

[4] Gilliland's Old Tuberculin, tested at intervals for potency.

[5] Very infrequently 0.1 mg. was injected if the 0.01 mg. elicited no reaction, and then 1.0 mg. if there was no reaction to 0.1 mg.

Clinic sessions were held in the evening to accommodate persons who otherwise would have been unable to attend the clinic.

The two full-time public health nurses were an invaluable aid in persuading the persons exposed to tuberculosis to attend the clinic and in expediting arrangements at the home of a patient going to an institution for treatment. In addition, they gave instructions to persons in the home regarding the care of the patient awaiting admission to the institution and the protection of those who were exposed.

These clinic procedures did not differ from those of any well run clinic.

MATERIAL

Records were accumulated on 502 families, including 25 individuals who lived alone, with a total population of 2,221 persons or an average of 4.4 persons per household. Table 1 gives the population of these 502 families according to sex, separating the first persons known to have manifest tuberculosis in the household (primary or source cases) from those exposed (contacts) to the disease. Persons with manifest disease were classified as manifest tuberculosis with tubercle bacilli in the sputum if their sputum was known to contain tubercle bacilli at any time during the course of their illness; persons who died from the disease were also included in this classification, because it was assumed that their sputum had contained tubercle bacilli. Persons with manifest disease with no known tubercle bacilli in their sputum included those whose sputum was never known to contain tubercle bacilli.

Persons exposed to manifest disease (contacts) were classified according to the status of the sputum of the primary case. One point, or exception, should be noted. There were 9 families in which the primary case had manifest disease with no known tubercle bacilli in the sputum, but subsequently a secondary case of manifest disease developed with tubercle bacilli in the sputum. There were 34 persons in these households who had contact with both the primary and the secondary cases and these were classified as persons exposed to manifest disease with tubercle bacilli in the sputum. The 9 secondary cases, however, were retained in the original classification and were counted as persons who developed clinical disease subsequent to the beginning of exposure to manifest disease with no known tubercle bacilli in the sputum. This procedure of retaining the secondary cases and transferring the other contacts to the category of persons exposed to tuberculosis with tubercle bacilli in the sputum had a tendency to raise the percentage of secondary cases among persons exposed to manifest disease with no known tubercle bacilli in the sputum.

The distribution of the population in the household according to sex, primary cases, and persons exposed to manifest disease is given in table 1. A few persons who were exposed only to manifest tuberculosis in an arrested stage or did not have any known exposure to tuberculosis are listed separately.

The table shows that in the total population the sexes were about equally represented, although the primary cases with tubercle bacilli in the sputum contained almost twice as many males as females; also, that persons exposed to tuberculosis with tubercle bacilli in the sputum accounted for over half (58.3 per cent) of the total population.

TABLE 1

Population of the households distributed according to sex, the first person known to have manifest disease in the household (primary case), and persons exposed to manifest disease (contacts)

	MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Primary cases with tubercle bacilli in the sputum	250	11.3	140	6.3	390	17.6
Persons exposed to manifest disease with tubercle bacilli in the sputum	574	25.8	720	32.4	1,294	58.3
Primary cases with no known tubercle bacilli in the sputum	57	2.6	62	2.8	119	5.4
Persons exposed to manifest disease with no known tubercle bacilli in the sputum	181	8.1	214	9.6	395	17.8
Persons exposed to arrested tuberculosis	3	0.1	5	0.2	8	0.4
No known exposure to tuberculosis	7	0.3	8	0.4	15	0.7
Total	1,072	48.2	1,149	51.7	2,221	100.2

Some of the groups included in this table were obviously too small to merit further attention and yet do not correspond closely enough to any other group to be a part of it. Those not considered further were the 25 persons with manifest tuberculosis who lived alone, 15 individuals who were not residents of any of these households but visited some of them as friends, 8 individuals who were exposed only to persons with arrested tuberculosis, and 15 individuals who did not have any known exposure to the disease. These deductions left 484 primary cases with manifest disease and 1,674 persons exposed to the disease.

Some of these persons exposed to manifest disease gave information indicating that their exposure had been initiated many years ago. The

person in the household who had the primary case may have died, but secondary cases had developed which brought the family to the clinic. Table 2 shows the contacts according to the type of their exposure and the year that it was initiated.

This table shows that 17.2 per cent of these persons began their exposure prior to 1925, 20.4 per cent from 1925 to 1929, and 62.4 per cent, or almost two-thirds, since 1930. Three-fourths of all these contacts were exposed to manifest disease with tubercle bacilli in the sputum.

When the first examination of any of these contacts revealed an asymptomatic lesion it was obvious that the time interval between the beginning of exposure and the development of the lesion was entirely

TABLE 2

Persons exposed to manifest tuberculosis according to the type of their exposure and the year it was initiated

YEAR WHEN EXPOSURE BEGAN	PERSONS EXPOSED TO MANIFEST TUBERCULOSIS					
	With tubercle bacilli in the sputum		With no known tubercle bacilli in the sputum		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
Prior to 1919	81	4.8	30	1.8	111	6.6
1920–1924	134	8.0	44	2.6	178	10.6
1925–1929	259	15.5	82	4.9	341	20.4
1930–1937	805	48.1	239	14.3	1,044	62.4
Total	1,279	76.4	395	23.6	1,674	100.0

unknown. A sharp distinction, therefore, was drawn between data obtained by history and by observation. The following data deal only with that portion of this group who were under direct observation. In some instances records were available, including a roentgenogram, that had been made in another institution before or subsequent to the examination at the New York Hospital. These records were utilized accordingly.

FIRST TUBERCULIN TEST AND FIRST EXAMINATION, INCLUDING A ROENTGENOGRAM OF THE CHEST, AMONG PERSONS EXPOSED TO MANIFEST TUBERCULOSIS

(Tested with tuberculin 962; examined roentgenographically 1,276)

Tuberculin tests were completed on 962 persons who were exposed to

manifest tuberculosis in the household. The results are given in tables 3 and 4. As a rule persons with manifest disease were not tested, hence the results apply for the most part to persons without manifest disease.

Table 3 presents the results of the tuberculin tests on 743 persons exposed to tuberculosis with tubercle bacilli in the sputum, and table 4 the results on 219 persons exposed to manifest disease with no known tubercle bacilli in the sputum.

Comparing these two tables, it is shown that only 12.5 per cent of the children under five years exposed to sputum-negative cases had a reaction as compared with 50.0 per cent in the group of contacts exposed to sputum-positive cases, and the percentage in the former group did not

TABLE 3

Results of the first tuberculin test of persons exposed to tuberculosis with tubercle bacilli in the sputum

AGE	NUMBER TESTED	REACTED TO 0.01 MG.				REACTED TO 1.0 MG. ONLY		NUMBER WITHOUT REACTION	TOTAL WITH REACTION	
		One plus	Two plus or greater	Total number	Per cent	Number	Per cent		Number	Per cent
0–4	56	10	11	21	37.5	7	12.5	28	28	50.0
5–9	102	19	44	63	61.8	9	8.8	30	72	70.6
10–14	131	36	69	105	80.2	11	8.4	15	116	88.5
15–19	119	53	46	99	83.2	11	9.2	9	110	92.4
20–29	107	48	48	96	89.7	8	7.5	3	104	97.2
30–39	73	39	28	67	91.8	5	6.8	1	72	98.6
40–49	87	35	46	81	93.1	6	6.9	—	87	100.0
50+	68	39	19	58	85.3	10	14.7	—	68	100.0
Total.....	743	279	311	590	79.4	67	9.0	86	657	88.4

rise above 90 among persons under forty years, a considerably later age than was found among persons exposed to tuberculosis with tubercle bacilli in the sputum.

Among both these groups of persons exposed to manifest tuberculosis (tables 3 and 4), approximately an equal percentage had a reaction to 1.0 mg. only; but among those exposed to manifest disease with no known tubercle bacilli in the sputum only 58.0 per cent showed a reaction to 0.01 mg. as compared with 79.4 per cent of those exposed to tuberculosis with tubercle bacilli in the sputum. Persons in the latter group were found to have a considerably higher percentage with a reaction to tuberculin in all age groups from birth to thirty-nine years of age. This was

especially noticeable among children less than ten years of age. The difference was confined largely to those who showed a reaction to 0.01 mg. of tuberculin.

At least one roentgenogram was secured on practically every person exposed to manifest disease who attended the clinic. Tables 5 and 6 show the results of the first examination, including the roentgenogram. The calcified nodules, latent infiltrations (childhood type), and latent apical tuberculosis (adult type) could be discovered *only* through the roentgenographic examination, while manifest (clinical) disease was discovered through the clinical examination of the patient in conjunction with the roentgenogram of the chest and other clinical aids.[6]

TABLE 4

Results of the first tuberculin test of persons exposed to tuberculosis with no known tubercle bacilli in the sputum

AGE	NUMBER TESTED	REACTED TO 0.01 MG.				REACTED TO 1.0 MG. ONLY		NUMBER WITHOUT REACTION	TOTAL WITH REACTION	
		One plus	Two plus or greater	Total number	Per cent	Number	Per cent		Number	Per cent
0–4	16	1	1	2	12.5	—	—	14	2	12.5
5–9	39	6	4	10	25.6	5	12.8	24	15	38.5
10–14	52	11	17	28	53.8	6	11.5	18	34	65.4
15–19	31	6	10	16	51.6	6	19.4	9	22	71.0
20–29	26	14	9	23	88.5	—	—	3	23	88.5
30–39	18	4	11	15	83.3	1	5.6	2	16	88.9
40–49	24	17	6	23	95.8	1	4.2	—	24	100.0
50+	13	6	4	10	76.9	3	23.1	—	13	100.0
Total.....	219	65	62	127	58.0	22	10.0	70	149	68.0

Table 5 shows that among 987 persons exposed to tuberculosis with tubercle bacilli in the sputum calcified nodules only were noted among person in all age groups, with a final percentage of 27.1. Among children

[6] Latent (asymptomatic) lesions of first infection or childhood type were designated as calcified nodules, and latent infiltrations, childhood; latent lesions of reinfection or adult type, as latent apical tuberculosis.

Manifest (clinical) tuberculosis, that which gives rise to physical signs or symptoms or both, was designated as childhood (first infection type) or adult (reinfection type) depending on the usual anatomical and clinical characteristics of the lesion.

Latent (asymptomatic) infiltrations of either the childhood or adult type could be active (progressive or retrogressive), but they were classified as asymptomatic until the patient had symptoms, or physical signs of disease were demonstrated. At that time the diagnosis was changed to manifest (clinical) disease.

under five years 6.2 per cent showed calcified nodules. The proportion was somewhat higher among persons between five and fourteen years of age than among older persons, but this may have been due partly to the presence of more serious lesions in the older persons which were given preference when observed in conjunction with calcified nodules.

Latent infiltration of the childhood type, with one exception, was found only in children less than ten years of age. Manifest tuberculosis

TABLE 5

Results of first examination, including a roentgenogram, of persons exposed to tuberculosis with tubercle bacilli in the sputum

AGE	NUMBER EXAMINED	CALCIFIED NODULES ONLY		LATENT INFILTRATION CHILDHOOD		LATENT APICAL TUBERCULOSIS		MANIFEST TUBERCULOSIS								TOTAL PERSONS WITH LESIONS	
								Childhood		Adult							
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Sp+	Sp−	Arrested	Other	Total	Per cent	Number	Per cent
0–4	64	1d	1.6	7	10.9	—	—	3a	4.7	—	—	—	—	—	—	15	23.4
		4	6.2														
5–9	112	33	29.5	3	2.7	—	—	1b	0.9	—	—	—	1	1	0.9	38	33.9
10–14	148	58	39.2	—	—	3	2.0	—	—	1	3	—	—	4	2.7	65	43.9
15–19	156	41	26.3	1	0.6	11	7.1	1c	0.6	4	7	—	—	11	7.1	65	41.7
20–29	167	42	25.1	—	—	11	6.6	—	—	14	13	2	—	29	17.4	82	49.1
30–39	112	21	18.8	—	—	17	15.2	—	—	3	4	—	—	7	6.2	45	40.2
40–49	127	33	26.0	—	—	25	19.7	—	—	1	10	2	—	13	10.2	71	55.9
50+	101	35	34.7	—	—	15	14.9	—	—	4	1	3	—	8	7.9	58	57.4
Total	987	1d	0.1	11	1.1	82	8.3	5	0.5	27	38	7	1	73	7.4	439	44.5
		267	27.1														

a = no tubercle bacilli found in the sputum; b = tubercle bacilli found in the sputum; c = manifest tuberculosis, arrested; d = enlarged caseous lymph nodes.

of the childhood type had the same distribution, with one person in the fifteen to nineteen year age group whose lesion was arrested.

Latent apical tuberculosis (adult) was observed among 2.0 per cent of persons between ten and fourteen years of age and among those in every subsequent age group. The highest percentage, 19.7, was recorded among those forty to forty-nine years of age. In general, latent infiltration (childhood) disappeared as latent apical (adult) tuberculosis appeared. Manifest tuberculosis of the adult type was recorded first in one individual in the five to nine year age group, who had arrested extrapulmonary disease.

Latent and manifest lesions of the adult type were found with equal frequency among persons between ten and nineteen years; but manifest disease was considerably more frequent among those twenty to twenty-nine years of age, and latent lesions were more frequent after the age of thirty years.

Among infants and young children, 23.4 per cent were found to have tuberculous lesions. This percentage increased steadily to 57.4 among persons over fifty years of age.

TABLE 6

Results of first examination, including roentgenogram, of persons exposed to manifest tuberculosis with no known tubercle bacilli in the sputum

AGE	NUMBER EXAMINED	CALCIFIED NODULES ONLY		LATENT APICAL TUBERCULOSIS		MANIFEST TUBERCULOSIS								TOTAL PERSONS WITH LESIONS	
						Childhood		Adult							
		Number	Per cent	Number	Per cent	Number	Per cent	Sp+	Sp−	Arrested	Other	Total	Per cent	Number	Per cent
0–4	20	—	—	—	—	2a	10.0	—	—	—	—	—	—	2	10.0
5–9	44	6	13.6	—	—	—	—	—	—	—	—	—	—	6	13.6
10–14	61	13	21.3	—	—	—	—	—	—	—	—	—	—	13	21.3
15–19	41	10	24.4	—	—	—	—	—	3	—	—	3	7.3	13	31.7
20–29	40	10	25.0	3	7.5	—	—	2	2	—	—	4	10.0	17	42.5
30–39	26	6	23.1	5	19.2	—	—	2	—	—	—	2	7.7	13	50.0
40–49	33	9	27.3	7	21.2	—	—	—	1	1	—	2	6.1	18	54.5
50+	24	7	29.2	2	8.3	—	—	1	1	4	—	6	25.0	15	62.5
Total	289	61	21.1	17	5.9	2a	0.7	5	7	5	—	17	5.9	97	33.6

a = no tubercle bacilli found in the sputum.

Among the 289 persons exposed to manifest tuberculosis with no known tubercle bacilli in the sputum, shown in table 6, calcified nodules were not observed in children under five years.

There were no instances of latent infiltrations of the childhood type. Manifest tuberculosis of the childhood type was found only in 2 under five years of age.

Latent apical tuberculosis (adult or reinfection type) was observed first among persons twenty to twenty-nine years of age, and was seen among those in all subsequent age groups, with the very high percentage of 21.2 among those forty to forty-nine years of age.

Manifest tuberculosis of the adult type was observed first in 7.3 per

cent of persons between fifteen and nineteen years of age. The highest percentage, 25.0, was recorded in those past fifty years of age.

The difference between the results of the examination of persons exposed to tuberculosis with tubercle bacilli in the sputum and with no known tubercle bacilli in the sputum was confined largely to persons under fifteen years of age. The final percentage with lesions in the former group was 44.5 and in the latter 33.6, a difference of 10.9 per cent which is statistically significant. With the exception of manifest tuberculosis of the childhood type the various lesions were observed at an earlier age and in general reached a higher percentage among the former group of contacts than among the latter. It should be noted that the number of persons exposed to tuberculosis with no known tubercle bacilli in the sputum was small, 289, or less than one-third of the number exposed to tuberculosis with tubercle bacilli in the sputum.

It is interesting to note that of persons exposed to tuberculosis with tubercle bacilli in the sputum 73 had manifest tuberculosis (adult type), 65 (89.0 per cent) of them having serious disease, while in only 8 (11.0 per cent) was it classified as arrested; whereas among persons exposed to manifest disease with no known tubercle bacilli in the sputum 17 had manifest disease, 12 (70.6 per cent) of them in a serious form, while in 5 (29.4 per cent) it was classified as arrested.

The ratio of manifest disease of the childhood type to that of the adult type given in these tables was approximately 1 to 13. Both asymptomatic (latent) infiltrations and manifest disease of the childhood type were, with two exceptions, observed only in children under ten years of age, and in one of these 2 cases the lesion was classified as arrested.

CORRELATION OF THE RESULTS OF THE TUBERCULIN REACTION AND THE EXAMINATION, INCLUDING A ROENTGENOGRAM, OF PERSONS EXPOSED TO MANIFEST TUBERCULOSIS

A correlation of the results of the tuberculin reaction and the examination, including a roentgenogram of the chest, of 954 persons exposed to manifest tuberculosis is given in table 7. Of these persons 736 were exposed to tuberculosis with tubercle bacilli in the sputum and 218 to tuberculosis with no known tubercle bacilli in the sputum, but in table 7 they are presented as one group.

Of these 954 persons, 714 (74.8 per cent) had a reaction to 0.01 mg. of tuberculin, and they were found to have the lesions as shown in table 7. A total of 333 persons (46.6 per cent) had lesions and 381 (53.4 per cent) did not.

There were 88 persons (9.2 per cent) of the total number, 954, who reacted to 1.0 mg. of tuberculin only. These 88 are enumerated as to their lesions in table 7. A total of 25 persons (28.4 per cent) had demonstrable lesions and 63 (71.6 per cent) had none.

Among these 954 contacts there were 152 who did not show a reaction to 1.0 mg. of tuberculin. Of these 152 persons 3.9 per cent had demonstrable calcified nodules and 1.3 per cent latent apical tuberculosis (adult type). There were no instances of latent infiltration, childhood type or of manifest disease.

It is apparent that among these persons, those who had a reaction to the smaller amount of tuberculin (0.01 mg.) were more likely to have demonstrable lesions (46.6 per cent) than those who showed a reaction

TABLE 7

Correlation between tuberculin reaction and results of examination, including a roentgenogram, of all persons exposed to manifest tuberculosis

REACTION TO TUBERCULIN	NUMBER EXAMINED	NO LESION		CALCIFIED NODULES ONLY		LATENT INFILTRATION				MANIFEST TUBERCULOSIS		TOTAL LESIONS	
						Childhood		Adult					
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Reacted to 0.01 mg....	714	381	53.4	251	35.2	6	0.8	55	7.7	21	2.9	333	46.6
Reacted to 1.0 mg. only.....	88	63	71.6	17	19.3	1	1.1	5	5.7	2	2.3	25	28.4
No reaction to 1.0 mg..	152	144	94.7	6	3.9	—	—	2	1.3	—	—	8	5.3
Total.....	954	588	61.6	274	28.7	7	0.7	62	6.5	23	2.4	366	38.4

only to the larger amount (28.4 per cent), and that the latter persons in turn were more likely to have demonstrable lesions than those who failed to show a reaction to the larger amount (5.3 per cent).

It was also true that persons who had a reaction to tuberculin were much more likely to have a serious lesion than those who failed to show a reaction, for of the 8 (5.3 per cent) persons who failed to show a reaction to 1.0 mg. of tuberculin 6 had calcified nodules only and 2 had latent apical tuberculosis.

Persons with obvious or severe manifest tuberculosis were not given the tuberculin test, which explains the small number with manifest disease.

If examinations, including a roentgenogram of the chest, had been made

only of those persons who showed a reaction to 0.01 mg. of tuberculin, 2 persons with manifest disease, 8 with latent infiltrations and 23 with calcified nodules only would have remained undiscovered. The first two types of lesions are obviously of much more importance than the last.

RESULTS OF THE FIRST AND LAST EXAMINATIONS, INCLUDING ROENTGENOGRAMS, AMONG PERSONS EXPOSED TO MANIFEST TUBERCULOSIS

Only persons who had at least two examinations, including a roentgenogram of the chest, with a minimum interval of six months between the examinations, are included in table 8. This table is of especial interest because it shows the diagnosis of 960 contacts at their first examination at the clinic and what occurred during the period of observation. The longest interval between the first and last examination was five years.

There are several rather striking features in this table. At the initial examination 442 of these contacts (46.0 per cent) already had a demonstrable lesion. This indicated that the exposure prior to examination had been sufficient to lead to the development of recognizable infection. There were 518 persons (54.0 per cent) with no lesions on first examination and 266 (27.7 per cent) with calcified nodules only. At the last examination only 4 of these persons had developed manifest disease.

The seriousness of asymptomatic infiltrations in children is shown by the fact that of the 9 persons with these lesions at their first examination 3 progressed to manifest disease, childhood type. Five eventually showed calcified nodules, and only one remained unchanged (asymptomatic). There were 57 persons with asymptomatic disease of the adult type (latent apical infiltration) which at the initial examination was restricted to the area between the apex and the level of the clavicle (latent I, II). Subsequently in 2 it progressed below the level of the clavicle but remained asymptomatic, while 3 developed manifest disease. Twenty-one persons had similar but more extensive asymptomatic lesions (latent III, IV), which extended from the apex to below the level of the clavicle at the initial examination. At the last examination 5 of these lesions had progressed to manifest disease and 16 remained unchanged. From the total of 87 persons with asymptomatic lesions at their initial examination (9 childhood and 78 adult type), 11 (12.6 per cent) progressed to manifest disease, and as would be expected a greater proportion of those

with the more extensive asymptomatic lesions at their initial examinations subsequently developed manifest disease than of those with the less extensive lesions.

TABLE 8

Results of first and last examinations including a roentgenogram of 960 persons exposed to manifest tuberculosis

FIRST EXAMINATION			DIAGNOSIS AT LAST EXAMINATION								CHANGE IN DIAGNOSIS SINCE FIRST EXAMINATION IN EACH GROUP	
Diagnosis	Number	Per cent of all contacts	No change	Calcified nodules only	Latent apical tuberculosis III, IV	Manifest tuberculosis					Number	Per cent
						Childhood type		Adult type				
						Sp. Neg.	Sp. Pos.	Arr.	Sp. Neg.	Sp. Pos.		
No lesion	518	54.0	515	1	—	—	—	—	1	1	3	0.58
Calcified nodules only	266	27.7	264	—	—	—	—	—	2	—	2	0.75
Enlarged lymph nodes, caseous	1	0.1	0	1	—	—	—	—	—	—	1	100.0
Latent infiltration												
Childhood type	9	0.9	1	5	—	2	1	—	—	—	8	88.9
Apical (adult)												
I, II	57	5.9	52	—	2	—	—	—	2	1	5	8.8
III, IV	21	2.2	16	—	—	—	—	—	3	2	5	23.8
Manifest tuberculosis												
Childhood												
Arrested	1	0.1	1	—	—	—	—	—	—	—	—	0.0
Sputum negative	4	0.4	4	—	—	—	—	—	—	—	—	0.0
Sputum positive	1	0.1	0	—	—	1	—	—	—	—	1	100.0
Adult												
Arrested	10	1.0	10	—	—	—	—	—	—	—	—	0.0
Sputum negative	43	4.5	23	—	—	—	—	7	—	13	20	46.5
Sputum positive	28	2.9	18	—	—	—	—	—	10	—	10	35.7
Extrapulmonary tuberculosis arrested	1	0.1	1	—	—	—	—	—	—	—	—	0.0
Total	960	99.9	905	7	2	3	1	7	18	17	55	5.7

Eighty-eight of these 960 persons (9.2 per cent) had manifest disease at their initial examination, demonstrating that exposure already had

exacted its most complete penalty. In 12 of them the disease was classified as arrested, and in 29 tubercle bacilli were found in the sputum. Their status did not show any conspicuous change at the time of their final examination, but it should be noted that this group does not include persons who were too ill to make more than one visit to the clinic or who died without making a return visit.

INFORMATION GATHERED BY BOTH HISTORY AND DIRECT OBSERVATION

The data presented thus far were collected under direct observation with little reference to the period before the family was registered at the clinic. In many of these households manifest disease was known to have been present prior to 1933, the year that the study began, as was shown in table 2. Through interrogation of various members of the family many data were collected which related to the interval between the date that manifest disease was first known to be present in the household and the date that the family came to the clinic. Such data pertained to deaths in the family from tuberculosis and other causes, and to the state of health of members of the household who were unable to attend the clinic or who refused to do so. It was learned that there were 27 persons who had developed manifest disease subsequent to the initiation of their exposure in the household in addition to the 112 who were examined in the clinic (tables 5, 6, 8).

Table 9 shows the number of persons exposed to manifest disease, *according to their age at the beginning of exposure*, and the number who subsequently developed manifest tuberculosis, *according to their age at the time of onset of their clinical (manifest) disease.*

The table shows that of 1,674 persons exposed to manifest disease in the household 139 (8.3 per cent) developed manifest disease at some time after the beginning of exposure. Of 345 persons who began their exposure between birth and four years of age, 27 (7.8 per cent) developed manifest disease by the time they were twenty-four years of age and 11 of them while still in the same age group in which their exposure was initiated. Of 598 persons who began their exposure between five and twenty years of age, 53 (8.9 per cent) subsequently developed manifest disease and, with the exception of one individual, before they were twenty-five years of age. These figures indicated that persons first exposed to tuberculosis between birth and twenty years of age developed manifest disease during a period of from fifteen to twenty years after the initiation of exposure. The closer their age approximated twenty years

when exposure was initiated the shorter was the period of time between the beginning of exposure and the onset of manifest disease.

Of 723 persons who began exposure when they were twenty years of age or older, 59 (8.2 per cent) developed manifest disease during a span of twenty years or more after the initiation of exposure. In general about one-half of those who developed manifest disease did so in the same decade as that in which their exposure was initiated, and the remainder during the following decade.

TABLE 9

All persons exposed to manifest tuberculosis and those who developed manifest disease distributed, according to their age at beginning of exposure and at onset of manifest disease

AT BEGINNING OF EXPOSURE			NUMBER AND AGE AT ONSET OF MANIFEST TUBERCULOSIS											DEVELOPED MANIFEST DISEASE	
Age	Number	Per cent of all contacts	0 to 4 yrs.	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 39	40 to 49	50 to 59	60 and over	Unknown	Number	Per cent persons exposed in age group
0–4	345	20.6	11	2	4	6	4	—	—	—	—	—	—	27	7.8
5–9	241	14.4	—	3	2	8	4	—	—	—	—	—	—	17	7.1
10–14	197	11.8	—	—	2	9	4	—	—	—	—	—	—	15	7.6
15–19	160	9.6	—	—	—	11	9	1	—	—	—	—	—	21	13.1
20–24	132	7.9	—	—	—	—	6	6	3	—	—	—	—	15	11.4
25–59	113	6.8	—	—	—	—	—	3	3	2	—	—	1	9	8.0
30–39	195	11.6	—	—	—	—	—	—	9	8	1	—	1	19	9.7
40–49	165	9.9	—	—	—	—	—	—	—	6	1	1	3	11	6.7
50–59	86	5.1	—	—	—	—	—	—	—	—	3	2	—	5	5.8
60+	32	1.9	—	—	—	—	—	—	—	—	—	—	—	—	—
Unknown	8	0.5	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	1674	100.1	11	5	8	34	27	10	15	16	5	3	5	139	8.3

It is interesting to note that of the 139 secondary cases 54 (more than one-third) developed manifest disease while still in the same age groups as at the beginning of their exposure. An additional 62 developed manifest disease during the ensuing ten years and 18 at a still later period. There were 8 persons whose age at the onset of their disease was not known.

These figures emphasize the long interval from the beginning of exposure to the onset of manifest disease. They also show the importance of an extended period of observation with reëxaminations of persons whose exposure begins in childhood, while for those first exposed between

the ages of ten and nineteen years more frequent reëxaminations are indicated if infection is to be detected and treated in its early stages (5).

Among these 139 secondary cases of manifest disease the age at onset of the disease was less than ten years in 11.5 per cent, between the ages of ten and thirty years in 56.8 per cent, and over thirty in 31.7 per cent. On the other hand, the age of the primary cases at the onset of manifest disease was less than ten years in only 1.2 per cent, between ten and thirty years in 40.9 per cent, and past thirty in 58.0 per cent. More than one-half of the primary cases developed manifest disease after the age of thirty while among the secondary cases two-thirds developed the disease prior to the age of thirty. This suggests that the primary cases were the result of exposure to manifest disease outside the family, whereas the secondary cases were probably caused by their exposure at home.

THE ANNUAL RECORDING (PERSON-YEARS) OF DATA FOR PERSONS EXPOSED TO MANIFEST TUBERCULOSIS

In order to calculate annual attack rates,[7] death rates from tuberculosis and the frequency rates[7] of manifest tuberculosis, the records had to be placed on an annual basis. The record of each person was started with the date of the beginning of exposure. All persons were classified as exposed to manifest disease either with tubercle bacilli in the sputum or with no known tubercle bacilli in the sputum and were placed in one of three age groups—birth to nine years, ten to fourteen years, fifteen years and over—according to their age when their exposure was initiated. Each individual was counted once each year following the beginning of exposure as long as information was available. Persons were dropped from the annual recording if they had left the household permanently. The year exposure began was designated the zero (0) year, hence, a record that extended over zero, one, two, etc. years after the beginning of exposure represented one, two, three, etc. person-years, counting the zero year as one.

Persons were registered as unexamined until they had had an examination, including a roentgenogram of the chest. During this period when they were unexamined they were given a diagnosis according to information obtained from other members of the family. This naturally was

[7] Attack rates are the percentages of persons who developed manifest disease in any stated interval and each individual is counted as a case only once, that is, for the interval in question; frequency rates, however, indicate the proportion of the group that have manifest disease in any given interval regardless of when the person developed manifest disease.

rather limited but accurate information could usually be secured stating whether the unexamined person was alive and known to have manifest tuberculosis or not. A death in the unexamined group was listed as due to tuberculosis or "other cause" as indicated by reliable evidence. A change in the diagnosis was entered in the year that it was made. If two diagnoses were made in one year, such as latent disease and later manifest disease, preference was given to the more serious lesion. Changes were recorded also of manifest disease from an active to an arrested stage, or of manifest disease with tubercle bacilli in the sputum to no tubercle bacilli in the sputum. Much information was secured from institutions that had examined or treated some of these people both before and after they were examined at the New York Hospital clinic.

This method of annual recording was the one used for the analysis of similar data assembled at the Henry Phipps Institute in Philadelphia (2, 3).

The person-year tables extended over a period of six years (0–5 inclusive) following the beginning of exposure. As shown in table 2 the majority of the contacts began their exposure after 1930, giving a maximum period of eight years from the beginning of exposure. By the end of the eighth year the number of persons counted in the various age groups had diminished very considerably. This reduction was due to the peripatetic habits of the city dweller and also to the fact that new families were registered year by year through 1937. In some of these new families manifest tuberculosis had been present only a short time and the persons exposed to manifest disease in the household had had a correspondingly short interval since the beginning of their exposure. For these reasons it seemed best to consider rates based on an interval of six years following the initiation of exposure.

Table 10 shows the number of persons who developed manifest tuberculosis at successive two-year intervals during a period of six years following the initiation of exposure and similarly the deaths from tuberculosis. The "person-years to onset of manifest disease" were used to calculate the attack rates and included all individuals until they developed manifest disease. Once an individual developed manifest disease that person was not counted subsequently, as the risk of attack no longer existed; but such persons were included in person-years of tuberculosis and in total person-years as persons with manifest disease, for they were still members of the total population and subject to the risk of death.

The total person-years were used to compute death rates and mean frequencies of manifest disease. The person-years of tuberculosis represented the number of persons with manifest disease in the population during the given interval. As can be seen, this figure is cumulative, for each individual was counted annually unless permanently removed from the household.

TABLE 10

Number of persons who developed manifest disease and the number who died from the disease and the number of person-years at successive two-year intervals following the beginning of exposure

YEARS SINCE BEGINNING OF EXPOSURE	PERSONS EXPOSED TO MANIFEST TUBERCULOSIS									
	With tubercle bacilli in the sputum					With no known tubercle bacilli in the sputum				
	Cases of tuberculosis	Person-years to onset of manifest disease	Tuberculosis deaths	Person-years of tuberculosis	Total person-years	Cases of tuberculosis	Person-years to onset of manifest disease	Tuberculosis deaths	Person-years of tuberculosis	Total person-years
Age at beginning of contact: 0–9 years										
0–1	5	814	1	5	814	1	316	1	2	317
2–3	7	673	1	9	675	1	271	—	2	272
4–5	2	552	1	12	562	1	224	—	1	224
0–5	14	2,039	3	26	2,051	3	811	1	5	813
10–14 years										
0–1	3	302	—	4	303	No tuberculosis				82
2–3	3	239	1	9	245					58
4–5	2	183	1	7	188					41
0–5	8	724	2	20	736					181
Over 15 years										
0–1	19	1,310	4	25	1,320	1	336	—	1	342
2–3	18	881	3	47	919	6	237	1	12	249
4–5	9	579	3	43	619	3	163	1	15	181
0–5	46	2,770	10	115	2,858	10	736	2	28	772

Table 9 recorded 139 secondary cases of manifest disease of whom 134 were of known age at the onset of their disease. Comparison of the data of tables 9 and 10 shows that 81 (60.4 per cent) of these persons developed manifest disease during the six-year interval following the initiation of exposure. Among those who began exposure between birth and nine years of age 44 eventually developed manifest disease (table 9) but only 17 (table 10), or slightly more than one-third, did so during the six-year period following the beginning of exposure.

Among those who began exposure between ten and fourteen years of age, 15 eventually developed manifest disease (table 9), and 8 (table 10), or slightly more than one-half, during the six-year period following the beginning of exposure. On the other hand, among those over fifteen years of age when exposure began, 75 ultimately developed manifest disease, and 56 or three-quarters of them during the interval shown in table 10. This indicated that, although many of the persons who ultimately developed manifest disease in the household were discovered during the six-year interval following the initiation of exposure, nevertheless a much longer period of observation would have been necessary to include all of them.

During this six-year interval there were 15 deaths from tuberculosis among those exposed to manifest tuberculosis with tubercle bacilli in the sputum and only 3 among those exposed to manifest disease with no known tubercle bacilli in the sputum. The total population and hence the total person-years of the former group of contacts was much larger than that of the latter.

It is interesting to note that some of these contacts developed manifest disease in each of the two-year periods following the beginning of exposure in all age groups, with the exception of those between ten and fourteen years of age who were exposed to manifest tuberculosis with no known tubercle bacilli in the sputum.

Table 11 gives the annual tuberculosis attack rates and the mean frequency of manifest disease for both New York and Philadelphia. The former were derived from the data in table 10, and the latter from data already published. Because the method of classifying the data of New York was slightly different from that used in Philadelphia the attack and death rates for the latter city were recomputed for purposes of comparison. The frequency rates are those given in the original publication (2). Only data pertaining to the six-year period following the initiation of exposure were utilized and the following discussion will be limited to the mean annual rates and frequencies for this period.

There was a striking degree of similarity in the mean annual rates of attack, death and frequency of manifest disease among those exposed to manifest tuberculosis with tubercle bacilli in the sputum in both cities during the six-year period. Among those whose exposure was initiated between birth and nine years of age the mean annual rates of attack and frequency of manifest disease were slightly lower in Philadelphia, 0.55 per cent and 0.65 per cent as compared with 0.69 per cent and 1.27 per

TABLE 11

Annual tuberculosis attack and death rates and the mean frequency of manifest disease among persons in Philadelphia and New York following exposure (a) *to tuberculosis with tubercle bacilli in the sputum and* (b) *to tuberculosis with no known tubercle bacilli in the sputum, by age when contact began*

YEARS SINCE BEGINNING OF CONTACT	PERSONS EXPOSED TO MANIFEST TUBERCULOSIS WITH TUBERCLE BACILLI IN THE SPUTUM					
	Philadelphia			New York		
	Tuberculosis					
	Attack rate Per cent	Death rate Per cent	Mean frequency Per cent	Attack rate Per cent	Death rate Per cent	Mean frequency Per cent
Age at beginning of contact: 0–9 years						
0–1	0.80	0.56	0.86	0.61	0.12	0.61
2–3	—	—	0.09	1.04	0.15	1.33
4–5	0.86	—	1.01	0.36	0.18	2.14
0–5	0.55	0.21	0.65	0.69	0.15	1.27
10–14 years						
0–1	1.17	—	1.14	0.99	—	1.32
2–3	0.70	—	3.87	1.26	0.41	3.67
4–5	0.95	0.46	4.96	1.09	0.53	3.72
0–5	0.96	0.12	3.11	1.10	0.27	2.72
Over 15 years						
0–1	1.75	0.38	2.30	1.45	0.30	1.89
2–3	1.90	0.24	4.17	2.04	0.33	5.11
4–5	2.73	0.85	8.28	1.55	0.48	6.95
0–5	2.03	0.45	4.40	1.66	0.35	4.02
WITH NO KNOWN TUBERCLE BACILLI IN THE SPUTUM*						
0–9 years						
0–1	0.24	0.12	0.24	0.32	0.32	0.63
2–3	0.14	—	0.65	0.37	—	0.74
4–5	—	—	0.64	0.45	—	0.45
0–5	0.14	0.05	0.45	0.37	0.12	0.62
Over 15 years						
0–1	1.11	—	1.41	0.30	—	0.29
2–3	0.93	—	2.18	2.53	0.40	4.82
4–5	1.53	0.58	4.31	1.84	0.55	8.29
0–5	1.16	0.15	2.43	1.36	0.26	3.63

* No manifest tuberculosis among persons from 10–14 years of age at beginning of exposure in either Philadelphia or New York groups.

cent respectively, and the death rate was higher, 0.21 per cent as compared with 0.15 per cent. Because of the very few deaths recorded for the New York group this difference may not be significant, but the data suggest that the disease may have been more acute among infants and children in Philadelphia.

Among those whose exposure was initiated between ten and fourteen years of age the mean annual attack rates and the mean frequency of manifest disease were approximately the same, 0.96 and 3.11 per cent in Philadelphia, 1.10 and 2.72 per cent in New York. The mean annual death rates were 0.12 per cent and 0.27 per cent respectively.

In both cities there were increases in all these mean annual rates when exposure was initiated at an older age. Among those whose exposure began after the age of fifteen years all rates reached their maximum mean annual percentage and were almost the same in both cities. The mean annual attack rate was approximately 2.0 per cent and the mean annual frequency of manifest disease about 4.0 per cent, while the mean annual death rate was 0.45 per cent in Philadelphia and 0.35 per cent in New York.

Among persons exposed to manifest tuberculosis with no known tubercle bacilli in the sputum those whose exposure began between birth and nine years of age had considerably lower mean annual rates of attack, death and frequency of manifest disease than those whose exposure began at the age of fifteen years and older. This was true of both New York and Philadelphia groups.

The rates of attack, death and frequency of manifest disease among those exposed to manifest tuberculosis with no known tubercle bacilli in the sputum were lower than corresponding rates among persons exposed to tuberculosis with tubercle bacilli in the sputum. This difference was more pronounced among those who were from birth to nine years of age at the beginning of exposure than among those who were fifteen years and older at the initiation of exposure and was characteristic of the group from each city.

Persons exposed to manifest tuberculosis with no known tubercle bacilli in the sputum in the New York group had higher mean annual rates of attack, death and frequency of manifest disease than were found in the Philadelphia group.

Although most of the data from Philadelphia were collected between 1924 and 1931 and those of New York between 1933 and 1937, the results indicated that the sequence of events following the initiation of

exposure to manifest tuberculosis in the household was practically the same.

The higher attack and frequency rates of manifest disease among persons exposed to tuberculosis with no known tubercle bacilli in the sputum for the New York group warranted further analysis. Among the 130 families in which the primary case was classified as manifest tuberculosis with no known tubercle bacilli in the sputum, there were 22 that had one secondary case each, and 2 others in which there were 2 and 4 secondary cases, respectively. The average age of 22 of these primary cases at the time the family was registered was forty-two years and the average duration of their illness was ten years. Their clinical picture was compatible with long standing chronic pulmonary tuberculosis, showing permanent, anatomical changes in the roentgenogram. After varying periods of observation 9 were classified as arrested. Numerous sputum examinations failed to demonstrate tubercle bacilli, although undoubtedly many had had sputum containing tubercle bacilli in the past and 15 had been under treatment for pulmonary tuberculosis. In no instance was there sufficient evidence to justify the statement that the sputum had been consistently free of tubercle bacilli throughout the course of their illness. Accordingly, they had to be designated as *sputum status unknown* or *no known* tubercle bacilli in the sputum.

Twenty-eight secondary cases of manifest tuberculosis had developed in these 24 households. At the time that the family was registered 6 of these 28 secondary cases had died and the average age of the remaining 22 was thirty-four years. The duration of illness of 3 was unknown, and the average of the remainder was 3.7 years. Sixteen, including the 6 that had died, were classified as manifest disease with tubercle bacilli in the sputum and 12 as manifest disease with no known tubercle bacilli in the sputum.

Some of the primary cases of those families were discovered because of the illness of the secondary case and some were found through surveys of persons on relief. They are important epidemiologically, for they can pass rather casual examinations without the disease being detected. No doubt their sputum did contain tubercle bacilli at intervals during the course of their illness, but at the time they were discovered the disease was literally "burnt out."

The high frequency of manifest disease among persons who began their exposure to tuberculosis at the age of fifteen years and older, and were exposed to tuberculosis with no known tubercle bacilli in the

sputum, may be attributed partly to insufficient data to classify accurately the status of the sputum of the primary case with the prolonged history of disease. It was also partly due to the loss of persons from the group of those exposed to tuberculosis with no known tubercle bacilli in the sputum because of their association with a secondary case that had tubercle bacilli in the sputum, discussed earlier (page 167).

RATIO OF PERSONS WITH MANIFEST DISEASE TO DEATHS FROM TUBERCULOSIS

Table 12 shows the total person-years accumulated by all the persons with manifest disease, together with the number of deaths from tubercu-

TABLE 12

Person-years of manifest tuberculosis, deaths and ratios of cases to deaths from tuberculosis among examined and unexamined primary and secondary cases

PERSONS WITH MANIFEST DISEASE AND DEATHS FROM TUBERCULOSIS	PRIMARY CASES		SECONDARY CASES		TOTAL CASES	
	Total	Minus arrested cases	Total	Minus arrested cases	Total	Minus arrested cases
Unexamined persons:						
Person-years of tuberculosis	2,015	1,867	268	242	2,283	2,109
Deaths from tuberculosis	136	136	20	20	156	156
Ratio of person-years to deaths	14.8	13.7	13.4	12.1	14.6	13.5
Examined persons:						
Person-years of tuberculosis	802	697	270	228	1,072	925
Deaths from tuberculosis	54	54	12	12	66	66
Ratio of person-years to deaths	14.9	12.9	22.5	19.0	16.2	14.0
Total persons:						
Person-years of tuberculosis	2,817	2,564	538	470	3,355	3,034
Deaths from tuberculosis	190	190	32	32	222	222
Ratio of person-years to deaths	14.8	13.5	16.8	14.7	15.1	13.7

losis recorded during the same period. The number of person-years contributed by primary and secondary cases is tabulated separately, and in each instance the total person-years are shown both including and excluding those years contributed by persons with manifest disease, arrested. The data for persons examined at the clinic and those not examined are given separately. Information regarding the latter was obtained from institutions where they had been treated and from relatives.

The person-years of tuberculosis equalled the number of years that the individuals with manifest tuberculosis were known to have been ill from the disease. This number divided by the total number of persons who died from tuberculosis gave the number of persons with manifest disease per death per year.

The table shows that person-years of tuberculosis and deaths from tuberculosis among the unexamined persons were more numerous than the corresponding number among the examined persons, indicating that the period of observation was quite short. The elimination of persons with arrested manifest disease did not alter the final figures to a great extent. The final ratio of 15.1 persons with manifest disease per annual death became 13.7 when arrested cases were excluded. A further analysis of these figures showed that the ratio of persons with manifest disease with tubercle bacilli in the sputum (open cases of tuberculosis) was 7 per annual death.

DISCUSSION

The purpose of the study of the New York families was to see whether events following exposure to manifest tuberculosis in this city differed from those observed in Philadelphia families similarly exposed. In spite of the fact that one study was closed before the other was initiated the results were surprisingly similar. This was particularly true of persons exposed to manifest tuberculosis with tubercle bacilli in the sputum. The only conspicuous difference was between the frequencies of manifest tuberculosis among persons exposed to manifest disease with no known tubercle bacilli in the sputum. Those for the New York group were considerably higher than the corresponding frequencies noted for the Philadelphia group. The reason for this difference is not entirely clear but various contributing factors with respect to the New York group have been discussed. The New York, as well as the Philadelphia data showed that disease followed exposure initiated at any age—infancy, adolescence or adult life.

The results of tuberculin tests and of roentgenological examinations of contacts in the New York group demonstrated that a higher percentage of those exposed to tuberculosis with tubercle bacilli in the sputum had a reaction to tuberculin and had tuberculous lesions than was found among those exposed to tuberculosis with no known tubercle bacilli in the sputum. This was particularly true of infants and young children. The percentage of persons with the more serious lesions

(asymptomatic infiltrations of the childhood or adult type and manifest disease of both types) was lower among persons exposed to tuberculosis with no known tubercle bacilli in the sputum; and again this was particularly true of persons in the younger age groups. These findings demonstrated that, following the beginning of exposure to manifest tuberculosis, the disease had been spread very widely among those exposed to it. The evidence of infection among the contacts varied from a reaction to tuberculin only, to manifest disease.

There was a correlation between the frequency of lesions and the intensity of the reaction to tuberculin, for only 5.3 per cent of those who failed to show a reaction had a demonstrable lesion as compared with 44.6 per cent of those with a reaction. It was also true that persons who had a reaction to the smaller dose of tuberculin (0.01 mg.) were more likely to have a serious lesion (asymptomatic or manifest disease) than those who had a reaction only to the larger dose (1.0 mg.).

Among all the contacts exposed to tuberculosis in these households 8.3 per cent had developed manifest disease. An additional 7.8 per cent of persons with roentgenological examinations were found to have asymptomatic infiltrations of the adult type (apical), and 0.9 per cent of the childhood type. Of the asymptomatic infiltrations of childhood or adult type observed in 87 persons 11 (12.6 per cent) progressed to manifest disease, an indication of their importance as forerunners of clinical disease.

The ratio of examined persons with manifest disease to deaths was 16 per year, and for persons with manifest tuberculosis with tubercle bacilli in the sputum (open cases) it was 7 per year.

The long interval between the age at the beginning of exposure and the age at onset of manifest disease of many of the secondary cases brings out the importance of a prolonged period of observation if persons with asymptomatic and manifest disease are to be detected early and treatment initiated at a time when it is most likely to be successful. Over one-half of the infants and young children who began their exposure in infancy and later developed clinical disease did so over a period of twenty years. On the other hand, among those who were from fifteen to twenty-five years of age at the initiation of exposure the onset of clinical tuberculosis occurred during a shorter interval. Also a higher percentage of these contacts developed manifest disease. More frequent examinations were indicated for these persons.

Persons who have been exposed to this disease should be warned not

to disregard either alarming or relatively harmless, persistent symptoms (5), but to consult their physician or clinic promptly. Even so, significant or even dangerous disease may be present which can be detected only by roentgenological examination, for the symptoms may be absent or trifling.

The roentgenographic examination is as important an adjunct in the disclosure of asymptomatic tuberculosis as a serological test in syphilis. Consequently, the discovery of asymptomatic or of manifest disease should lead to an examination, including a roentgenogram of the lungs, at least of those persons who are living in the same household.

Such a survey will furnish some basis for determining how frequently examinations should be made. The discovery of infants and children with severe reactions to tuberculin, of persons with asymptomatic lesions of childhood or adult type, or of secondary cases of manifest disease indicates the degree of infection that has already occurred. Children between the ages of five and ten years do not need as frequent examination as those under five years. When the contacts reach adolescence and young adulthood the frequency of examinations should be increased. A person may develop manifest disease a few months after a roentgenographic and clinical examination has given no indication that clinical disease was imminent, but it is believed that the majority of persons will show an asymptomatic lesion prior to the advent of clinical disease.

The status of the sputum of cases in the household should affect the frequency of examinations. Persons exposed to tuberculosis with tubercle bacilli in the sputum should be examined more frequently than those exposed to the disease with no known tubercle bacilli in the sputum.

Arbitrarily, one examination a year including a roentgenogram of the lungs may be adopted as a minimum. This number should be increased as the situation in the household requires it.

It is important to note that these observations were made on a white population and do not apply to colored persons.

SUMMARY

A survey followed by a period of observation of persons exposed to manifest (clinical) tuberculosis in families in New York was carried out during 1933–1938. Comparisons were made with the results of a similar study previously conducted in Philadelphia.

The results may be summarized as follows:

1. More persons showed a reaction to tuberculin (88.4 per cent)

among those exposed to tuberculosis with tubercle bacilli in the sputum than was found among those exposed to tuberculosis with no known tubercle bacilli in the sputum (68.0 per cent). The greatest difference was observed among children under five years of age (50.0 per cent as compared with 12.5 per cent respectively).

2. Similarly, more persons were found to have tuberculous lesions, 44.5 per cent with calcified nodules, asymptomatic infiltrations or manifest disease among those exposed to tuberculosis with tubercle bacilli in the sputum than were observed, 33.6 per cent, among those exposed to the disease with no known tubercle bacilli in the sputum. The difference was most conspicuous among persons under fifteen years of age.

3. The frequency of persons with tuberculous lesions among those who had a reaction to 0.01 mg. of tuberculin was greater (46.6 per cent) than that observed among those who showed a reaction to 1.0 mg. only (28.4 per cent). Among those who failed to show a reaction 5.3 per cent had lesions.

4. Asymptomatic infiltrating lesions were found to be significant as a forerunner of manifest disease, for of 87 contacts with these lesions at their initial examination 11 (12.6 per cent) progressed to manifest disease.

5. Among 1,674 persons exposed to the disease 139 (8.3 per cent) had developed manifest disease at various intervals during a period of twenty-five years following the beginning of their exposure. This period was considerably shorter among adolescents and young adults.

6. The mean annual attack, death, and frequency rates over a six-year period following the beginning of exposure among persons exposed to manifest tuberculosis with tubercle bacilli in the sputum were quite similar in New York and Philadelphia. The frequency of manifest disease in persons exposed to tuberculosis with no known tubercle bacilli in the sputum, among persons fifteen years of age and over, was higher in New York than that observed in Philadelphia.

7. Among examined persons the ratio of cases to deaths in the New York group was 16 per year; for persons with open tuberculosis it was 7.

CONCLUSIONS

That tuberculous infection spreads from persons with manifest disease to those exposed in the household was shown by the high percentages of persons with a reaction to tuberculin, with asymptomatic lesions and

with manifest disease. Infection was particularly evident among those exposed to tuberculosis with tubercle bacilli in the sputum.

Manifest disease developed among those exposed to it regardless of the age at which exposure was initiated.

These observations are in accord with those previously made among persons exposed to the disease in Philadelphia households.

Persons exposed to manifest disease should be kept under observation over a long period of time if asymptomatic and clinical disease are to be detected early.

SUMARIO

En el período 1933–1938 se llevó a cabo un estudio, seguido de un período de observación, en las personas expuestas a tuberculosis (clínica) manifiesta en ciertas familias de Nueva York, comparándose el resultado con el obtenido en un estudio semejante llevado a cabo previamente en la ciudad de Filadelfia.

El resultado puede sumarizarse así:

1. Entre los expuestos a la tuberculosis cuando el esputo contenía bacilos tuberculosos, fué mayor el número de personas (88.4 por ciento) positivas a la tuberculina, que entre los expuestos a la tuberculosis cuando el esputo no contenía, en lo que se sepa, bacilos tuberculosos (68.0 por ciento). La diferencia mayor correspondió a los niños de menos de cinco años (50.0 por ciento, comparado con 12.5 por ciento, respectivamente).

2. En forma semejante, entre los expuestos a la tuberculosis cuando el esputo contenía bacilos tuberculosos, se encontraron más personas (44.5 por ciento) con lesiones tuberculosas, ganglios calcificados, infiltraciones asintomáticas o enfermedad manifiesta, que entre los expuestos a la enfermedad cuando el esputo no contenía, en lo que se supiera, bacilos tuberculosos (33.6 por ciento). La diferencia fué más notable entre las personas de menos de 15 años.

3. El número de personas que tenían lesiones tuberculosas fué mayor (46.6 por ciento) entre las que acusaban una reacción positiva a 0.01 mg. de tuberculina, que entre las que no reaccionaban más que a 1.0 mg. (28.4 por ciento). Entre los que no reaccionaron, 5.3 por ciento tenían lesiones.

4. Las lesiones infiltrantes asintomáticas revelaron importancia como signos premonitorios de la enfermedad manifiesta, pues de 87 contactos que las manifestaron en su examen inicial, 11 (12.6 por ciento) siguieron evolucionando hasta manifestar enfermedad declarada.

5. Entre 1,674 personas expuestas al mal, 139 (8.3 por ciento) habían revelado enfermedad manifiesta a varios plazos durante un período de veinticinco años transcurridos desde que comenzó su exposición. Este período fué mucho más breve entre los adolescentes y adultos jóvenes.

6. En los estudios de Nueva York y Filadelfia fueron muy semejantes los pro-

medios anuales de ataques, mortalidad y morbidad durante el período de seis años consecutivo al comienzo de la exposición entre las personas expuestas a tuberculosis manifiesta cuando el esputo contenía bacilos tuberculosos. La frecuencia de enfermedad manifiesta en las personas expuestas a la tuberculosis cuando el esputo no contenía en lo que se supiera bacilos tuberculosos fué, sin embargo, mayor entre las personas de 15 años o más en Nueva York que en Filadelfia.

7. Entre los sujetos estudiados, la proporción anual de casos en relación con muertes fué de 16 por 1 en el grupo de Nueva York; en los enfermos con tuberculosis abierta, fué de 7.

The authors wish to express their appreciation to Dr. Eugene L. Opie for his helpful suggestions and criticisms.

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TRANSIENT PULMONARY INFILTRATIONS[1]

A Case with Eosinophilia (Loeffler's Syndrome) Associated with Amoebiasis

AMANDA HOFF AND H. MASON HICKS

Since 1931, when Loeffler (1) first described transient pulmonary infiltrations with blood eosinophilia, there have been relatively frequent reports of cases, all of which have shown so striking a similarity in symptomatology, physical and X-ray findings that a definite entity has been recognized to which the name of "Loeffler's Syndrome" has been given.

Loeffler, in attempting to differentiate the infiltrations from early tuberculosis, noted the transience of the pulmonary consolidations, the frequent presence of an eosinophilia, ranging from 10 to 60 per cent, and the spontaneous disappearance of the symptoms and signs. He also reported recurrence of the entire picture in one patient. He did not, however, stress the possible allergic nature of the condition although recognizing the probable presence of various aetiological agents.

Subsequent case reports have practically all demonstrated that Loeffler's syndrome is probably the pulmonary manifestation of an underlying allergic condition which may be brought about by various allergens.

Many of the cases reported (2, 3) have been in individuals, often children, whose allergic symptoms, such as vasomotor rhinitis and especially asthma, lead to investigation by X-ray and the consequent discovery of the pulmonary infiltrations.

The exact cause of the allergic symptomatology has been determined in surprisingly few cases—in one (3) there was a history of the passing of a helminth (ascaris) which, however, occurred two years before the appearance of pulmonary symptoms and which was not thought to be relevant. There have also been a few other instances of ascaris infestations coinciding with Loeffler's syndrome.

Stefano (4) reports a case of recurring asthmatic attacks in which transient areas of pulmonary infiltrations were demonstrated by X-ray and in which amoebae were found in the sputum but not in the stools. Both amoebae and asthma disappeared after emetine therapy.

Soderling (3) cites an epidemic of transient pulmonary infiltrations

[1] From Bellevue Hospital, New York City.

reported by Engel of Shanghai in 1935—the epidemic coincided with the pollination of a plant (privet) and was thought to be an allergic response to it. These cases showed the characteristic X-ray picture, eosinophilia up to 15 per cent and a slightly elevated sedimentation rate. Engel also noted that the patients in his series complained that their sputum had a distinctly metallic taste. A very interesting instance of parasitic infestation in which the typical pulmonary infiltrations were noted was that reported by Lavieri, Bariety and Caroli (5). Their case, one of infestation with *Fasciola hepatica*, showed a very high eosinophile count (69 per cent) and the authors observe that the parasitic infestation may be partly responsible for this reaction. They also discuss the possibility of a parasitic cause for certain cases of transient pulmonary infiltrations.

Most cases of Loeffler's syndrome may then be considered allergic in origin, the allergens being as variable as those giving rise to other allergic manifestations. The syndrome in a typical case consists of attacks of asthma accompanied by cough, by the common occurrence of eosinophilia, which may be as high as 60 per cent or may rarely be absent (as in other allergic conditions), and by the presence of a low-grade fever accompanied by mild leucocytosis and a slightly elevated sedimentation rate. Physical examination is usually negative except for the pulmonary signs which are remarkably few and which usually consist only of a few moist and sibilant râles over the areas of consolidation.

The characteristic X-ray picture, which has been well described by Loeffler, and also by Breton in 1938 (6), consists of consolidations which appear suddenly in various parts of the lung and disappear rapidly only to reappear in another portion of the lung. The shadows are most frequently found in the lower lung field near the diaphragm and vary in size. They disappear in approximately a week and usually leave only very fine fibrous star-shaped scars.

The case here reported is presented as one of Loeffler's syndrome in which the probable aetiological factor has been found and eliminated.

CASE REPORT

R. M., white female, forty years of age, was first seen August 7, 1939. Her chief complaint was a violent paroxysmal cough of three months' duration. The cough was nonproductive except on rare occasions when she had raised a small amount of thin, mucoid sputum. Gradually the cough had increased in severity and frequently ended in vomiting. She had noted a distinctly metallic taste during this period. Her past history was negative except for one attack of

pyelitis while on a business trip to Chicago in 1931. Her mother had had an eczema with eosinophilia. There was no other history of allergy.

Physical examination was essentially negative. Temperature, pulse and respirations were normal. Sinuses were clear by transillumination and by X-ray. The throat was negative. The chest showed a slightly prolonged expiration throughout. Lung fields were clear on fluoroscopy. The abdomen was negative. The liver and spleen were not palpable, nor did they percuss enlarged.

Patient was advised to rest more and to collect sputum for examination. During this period the paroxysmal cough increased, the metallic taste persisted and slight dyspnoea appeared. Mouth temperature ranged between 99° and 101.4°F. On August 14, 1939 an occasional sibilant râle was heard posteriorly and breathing was asthmatic in character. Sputum examinations were negative for tubercle bacilli. Sedimentation rate was 28 mm. in one hour (Cutler); haemoglobin 65 per cent; red count 4,060,000; color index 0.81; white count 12,280 with a differential count showing eosinophiles 19.5 per cent, polynuclears 46 per cent; lymphocytes 33 per cent; transitionals 1 per cent. Chest plates (figure 1) at this time showed a triangular shadow extending outward from the right hilum past the middle of the lung field. The triangle was about 5 x 7 cm. A right lateral film showed a horizontal

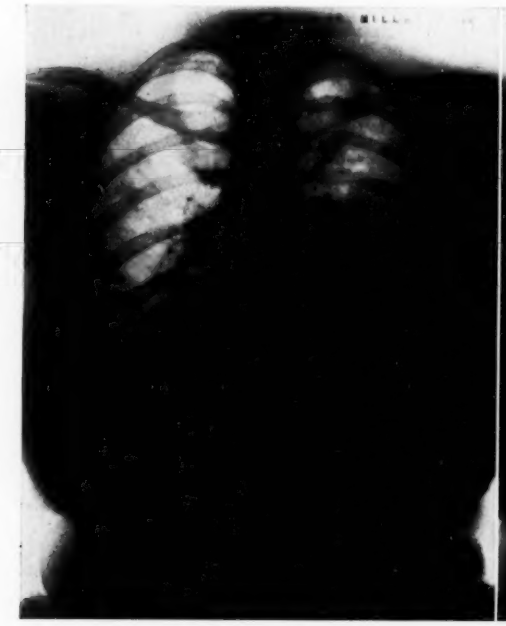

FIG. 1. August 14, 1939

FIG. 2. August 31, 1939

margin and formed a triangle 3 cm. in altitude by 10 cm. in anteroposterior diameter. There was clouding of the right base laterally and anteriorly. A diffuse density was present in the left second intercostal space.

The patient was kept on bed-rest. She continued running a low-grade febrile course, the paroxysmal coughing continued and its severity was not lessened. She complained of a dull ache over the region of the liver. There was slight shock tenderness over the right lower ribs posteriorly. Scattered sibilant râles persisted. On August 31, 1939 the sedimentation rate remained at 28 mm.; haemoglobin 69 per cent; red cells 4,130,000; white cells 15,200 with 41 per cent eosinophiles. Repeated sputum examinations remained negative for tubercle bacilli. The specimens consisted of a moderate amount of viscid, mucoid, opalescent, homogeneous sputum. Chest plates (figure 2) at this time showed that the triangular shadow noted seventeen days previously had almost completely disappeared, also a small amount of the cloudiness in the second left intercostal space had disappeared. There was, however, a shadow at the right base medially and anteriorly about 4 x 3 cm. and there was a diffuse mottling at the left base which was not present previously.

A more detailed history at this time revealed that, during the so-called attack of pyelitis while in Chicago in 1931, her chief symptom was a profuse, bloody diarrhoea lasting about ten days. The stools were not examined and she had received only symptomatic treatment. There had been no other attacks.

On September 2, 1939, examination of the stools showed numerous *Endamoeba histolytica* cysts. The patient was placed on "anayodin" (oxyquinolin-sulphonic acid plus 30 per cent iodine and sodium bicarbonate) for two weeks and, then, a course of emetine hydrochloride was given, 1 cc. intramuscularly for seven days. During the treatment with "anayodin" there was slight improvement. The temperature came down to normal and the paroxysms of coughing decreased. The aching pain in the region of the liver persisted. The response during the injections of emetine hydrochloride was dramatic. After the fifth day the cough, dyspnoea, metallic taste and pain over the right upper abdomen entirely disappeared. The physical examination was entirely negative. Stool examinations for amoebic cysts were negative. On September 20, 1939 the percentage of eosinophiles was down to 16 per cent and white count was 8,000. The haemoglobin rose to 86 per cent and the sedimentation rate was 14 mm. On September 26, 1939 the chest plate was entirely clear. The patient returned to work on October 10, 1939 and has remained perfectly well.

DISCUSSION

The symptomatology of our case fits in perfectly with that of other reports of the condition. In connection with this symptomatology it is

interesting to note that the patient complained of a metallic taste which was also reported in the Shanghai epidemic of Engel. The assumption in this epidemic that the condition was a manifestation of plant allergy was not definitely proved, and there is opportunity for conjecture as to whether the examination of stools and sputa might not have revealed the presence of amoebae in some of the cases, as amoebiasis is not uncommon in China.

The presence of amoebiasis is of importance both as to a consideration of the aetiology of the syndrome and as to the rôle specific therapy may play. The fact that the asthmatic attacks in our patient had lasted three months without improvement and the appearance of symptoms referable to the liver, which made an early amoebic hepatitis a possibility, made us wonder whether or not the pulmonary infiltrations would have cleared up without specific therapy. As the patient had never previously had asthma or other allergic manifestations her response to the presence of amoebae seems to indicate that they were the specific allergens causing her symptoms.

Specific treatment cleared up the amoebiasis, and the dramatic disappearance of all signs and symptoms following the unusual persistence of pulmonary symptoms for three months further suggests the specificity of *E. histolytica* as the aetiological agent.

SUMMARY

Loeffler's syndrome as the pulmonary manifestation of an allergy is discussed and the literature pointing to this conclusion is reviewed. The clinical picture is presented, and a case associated with amoebiasis is reported in detail. In conclusion the importance of transient pulmonary infiltration as an allergic response to a specific allergen is again emphasized and a thorough investigation of the patient for the aetiological factor is urged. The discovery of such an agent may indicate the need for specific therapy before the patient can be restored to health.

SUMARIO

Discútese el síndrome de Loeffler como manifestación pulmonar de una alergia, y se repasa la literatura que justifica esta conclusión. Discútese el cuadro clínico, y comunícase con todo detalle un caso asociado con amibiasis. Al concluir, recálcase de nuevo la importancia de la infiltración pulmonar transitoria como reacción alérgica a un alergeno específico y se recomienda una investigación detenida del enfermo en cuanto al

factor etiológico. El descubrimiento de un agente de ese género, puede indicar la necesidad de la terapéutica específica antes de poder devolver la salud al enfermo.

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TWO SEPARATE SPECIFIC IMMUNE PHENOMENA IN TUBERCULOSIS[1,2]

A Concrete Demonstration

H. J. CORPER AND MAURICE L. COHN

In spite of the discovery of the tubercle bacillus almost six decades ago and the advocacy and periodic withdrawal of tuberculin therapy since the early nineties, tuberculosis still remains a scientifically unsolved problem and one in which clinical observations have always had to depend upon animal experimentation for the ultimate answer regarding the mechanism involved that may justify or decry the clinical application of therapies. The clinician to-day is still confronted with the evaluation of specific tuberculo-immunity in man and hesitates when tuberculin is considered for treatment. Even contemporary clinical observers are divided in two separate groups—those who believe in the beneficial features of specific tuberculo-immunity and specific tuberculo-allergy, and those who believe these to be detrimental. There have been no conclusive clinical investigations to prove either faction correct, nor can these controversial questions be solved definitely by any means known to the clinician.

Until recently, leading laboratory investigators, strong advocates of the immune conception (Paul Roemer, 1904–1912; Allen Krause, 1920–1926; Albert Calmette, and others), viewed specific tuberculo-immunity and specific tuberculo-allergy as different manifestations of the same biological phenomenon. Since 1936 (1) we have shown the existence of specific tuberculo-immunity but are unable to gauge its extent in man accurately by any known means; while in animals there is only one reliable criterion of its extent, and that is actual infection. So also, in accurate biological analyses it was shown that tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity are separate and apparently unrelated biological phenomena (2). Specific tuberculo-anaphylaxis apparently is of no significance in tuberculosis (3), while the intoxication is closely related to specific tuberculo-allergy whether caused by tuber-

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This investigation was aided by a gift from Morton May in memory of Florence G. May.

culin (the liberation of which in the body is questioned) or by bacillary bodies. Desensitization with filtrate (tuberculo-protein) to the skin reaction (tuberculin) exerts no influence on the specific tuberculosis immunity (4). Such desensitization protects against lethal general tuberculo-allergic intoxication (5). Thus far, by accurate analytical biological studies, utilizing pure tuberculo preparations (6) and various types of tubercle bacilli (avirulent (7) and virulent), it has been possible to define and differentiate individually these various phenomena (tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity) which might play a part in tuberculosis in man. Without the preliminary observations, it would have been impossible to correlate these phenomena or to evaluate them practically and build them into a unified picture which could be put into a concrete experimental demonstration embodying the main features of these phenomena. In such an evaluation, it must be remembered that the specific tuberculo-immunity in its broadest sense is a relative phenomenon, potent, however, throughout the entire range of infection possibilities when viewed properly. It retards tuberculosis, definitely evaluated on a pathological basis, and it prolongs the life of the infected host markedly when other extraneous factors are excluded or avoided. It is the prolongation of life as well as the retardation in the tuberculosis in all cases that make this phenomenon interesting clinically. To avoid the pitfalls of intercurrent conditions, such as may not be regular but may prove serious, introduces another practically significant feature. This is the problem of tuberculo-allergy.

EXPERIMENTAL

The tuberculo-allergic feature: In earlier studies on the tuberculo-allergic reactions, it was found that, in order to elicit a lethal allergic reaction, a definite degree of sensitization or tuberculous involvement was required as well as a definite amount of intoxicating material (4) had to be injected at a certain time. Therefore, in order to present the significance of tuberculo-allergy in the tuberculo-immune reaction, produced by viable avirulent human tubercle bacilli, and the protection offered against this toxic allergic effect by tuberculo-allergic desensitization or immunization, three sets of guinea pigs, 8 in each set, were apportioned into: (*a*) a control group given only an intravenous (ear vein) infecting injection of a fine suspension of 1.0 mg. of highly virulent viable human tubercle bacilli (# 160); (*b*) an immune group was given a subcutaneous injection of 1.0 mg. of avirulent viable human tubercle bacilli one month

prior to the same intravenous infecting injection received by the control group; and (*c*) a third group was treated the same as the second, immune group, except that desensitization or immunization to tuberculo-allergy, with 1 cc. 1:10 natural filtrate (tuberculo-protein) intravenously, was begun one week after the tuberculo-immunizing subcutaneous injection of the avirulent bacilli, repeated every fifth day for a total of five injections during twenty days, and terminated five days before the virulent intravenous infection. During the entire experimental period, the animals were weighed regularly, and every precaution was taken to avoid extraneous hazards to their health or nutrition so that the death records would be as nearly as possible a gauge of the tuberculous condition of the animals. The results of the weight records and the day of natural death of the three groups of animals are recorded in chart 1.

The duration of life of the intravenously infected *controls* was 11, 15, 16, 16, 17, 18, 18 and 18 days, with an average of sixteen days; the *specific immune* guinea pigs lived 19 hours, 36 hours, 8, 9, 17, 19, 22 and 28 days after virulent infection, with an average life duration of only thirteen days; and the *specific immune and tuberculo-allergic desensitized or immunized* guinea pigs lived 17, 19, 22, 23, 23, 24, 26 and 27 days, an average duration of life of twenty-three days.

This experiment points out the disastrous effect of tuberculo-allergy developing coincidently with the tuberculo-immunity when heavy intravenous infections occur resulting in lethal shock intoxication. When the tuberculo-allergy is excluded to some extent to avoid intoxication by proper tuberculo-allergic desensitization or immunization, however, the full effect of the specific immunity can exert itself to establish a pronounced and definite prolongation of life from an average of sixteen days in the controls to twenty-three days for the immune and treated guinea pigs. The pathological findings of this experiment, which are to be recorded elsewhere in detail (8), showed that the animals dying early as a result of the intravenous injection of large amounts of virulent human tubercle bacilli disclosed, as would be expected, very little discrete

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CHART 1. The effect of specific tuberculo-immunity on the duration of life of heavily intravenously infected guinea pigs and the part played by tuberculo-allergy. The weight curves end on the day of death and begin when the "immune" guinea pigs were given 1 mg. avirulent tubercle bacilli; "T" = tuberculin given seven days later and continued through the twenty-seventh day; the "immune and treated" in addition to specific immunization were desensitized against allergy; and "INF" = 1.0 mg. virulent human tubercle bacilli given intravenously for infection on the thirty-second day.

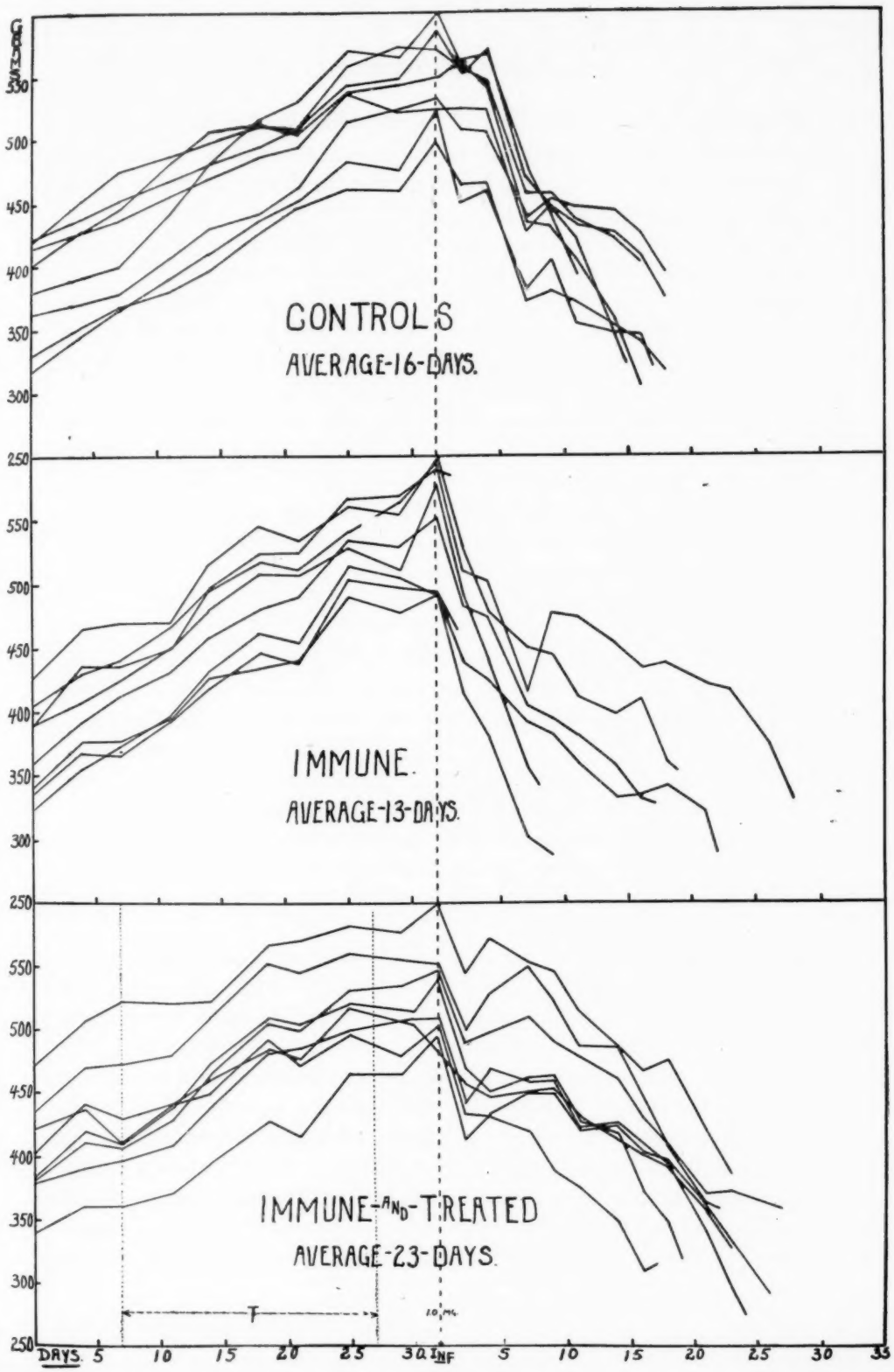
CONTROLS
AVERAGE-16-DAYS.
IMMUNE.
AVERAGE-13-DAYS.
IMMUNE-AND-TREATED
AVERAGE-23-DAYS.
T
INF
DAYS.

CHART 1

tuberculous disease. But they did show rather predominant evidences of an acute toxicity centered about the general allergic reaction, and yet it was not sufficiently pronounced to present the characteristics of a local reaction resulting from the local injection of a sufficient amount of tuberculin to provoke evident tissue changes. The changes noted proved to be more of a secondary character (pulmonary emphysema and congestion of the other organs) in the animals dying early, while later the reaction to the bacilli in the organs obscured this picture to the extent that definition was impossible. It can be assumed from other evidence also presented that the animals that died within the first ten days following the intravenous infection died either from the consequences of the violent specific allergic response or a combination of this with the rapidly developing tuberculosis. It is to be noted from chart 1 that neither the specific tuberculo-immunization with the viable avirulent human tubercle bacilli nor the tuberculo-allergic desensitization or immunization as performed exerted any appreciable detrimental effect on the guinea pigs. This is evident from the weight curves and general condition of the animals.

In order to exclude the marked detrimental and lethal effect of the virulent bacillary intravenous infection as displayed when the larger amount of viable tubercle bacilli is given intravenously, the experiment was repeated in all essential details except that the intravenous infecting dose of viable virulent human tubercle bacilli was reduced to 0.01 mg. The results of these observations are disclosed in chart 2.

The duration of life of the intravenously infected *controls* given only 0.01 mg. of viable virulent human tubercle bacilli was 20, 24, 35, 35, 37, 39, 41 and 43 days, with an average of thirty-four days; the *specific immune* guinea pigs lived 37, 41, 47, 52, 54, 56, 68 and 83 days, with an average life of fifty-five days; and the *specific immune and tuberculo-allergic immunized* guinea pigs lived 42, 46, 46, 47, 49, 50, 54 and 66 days, an average duration of life of fifty days. Chart 2 corroborates the findings in chart 1, in that there is a definite prolongation in the life (average fifty days as compared with the control average of thirty-four days) of the specific immunized guinea pigs that have been immunized also against tuberculo-allergy. When the tuberculo-allergic intoxication does not appear, made manifest by the absence of early allergic deaths among the specific immunized guinea pigs not receiving a large enough infecting amount of bacilli, the duration of life (average fifty-five days) closely approximates in the two groups showing neither a beneficial nor

infection was initiated by the intravenous injection of virulent tubercle bacilli thirty-two days after specific immunization. Death is indicated by the termination of the weight curve.

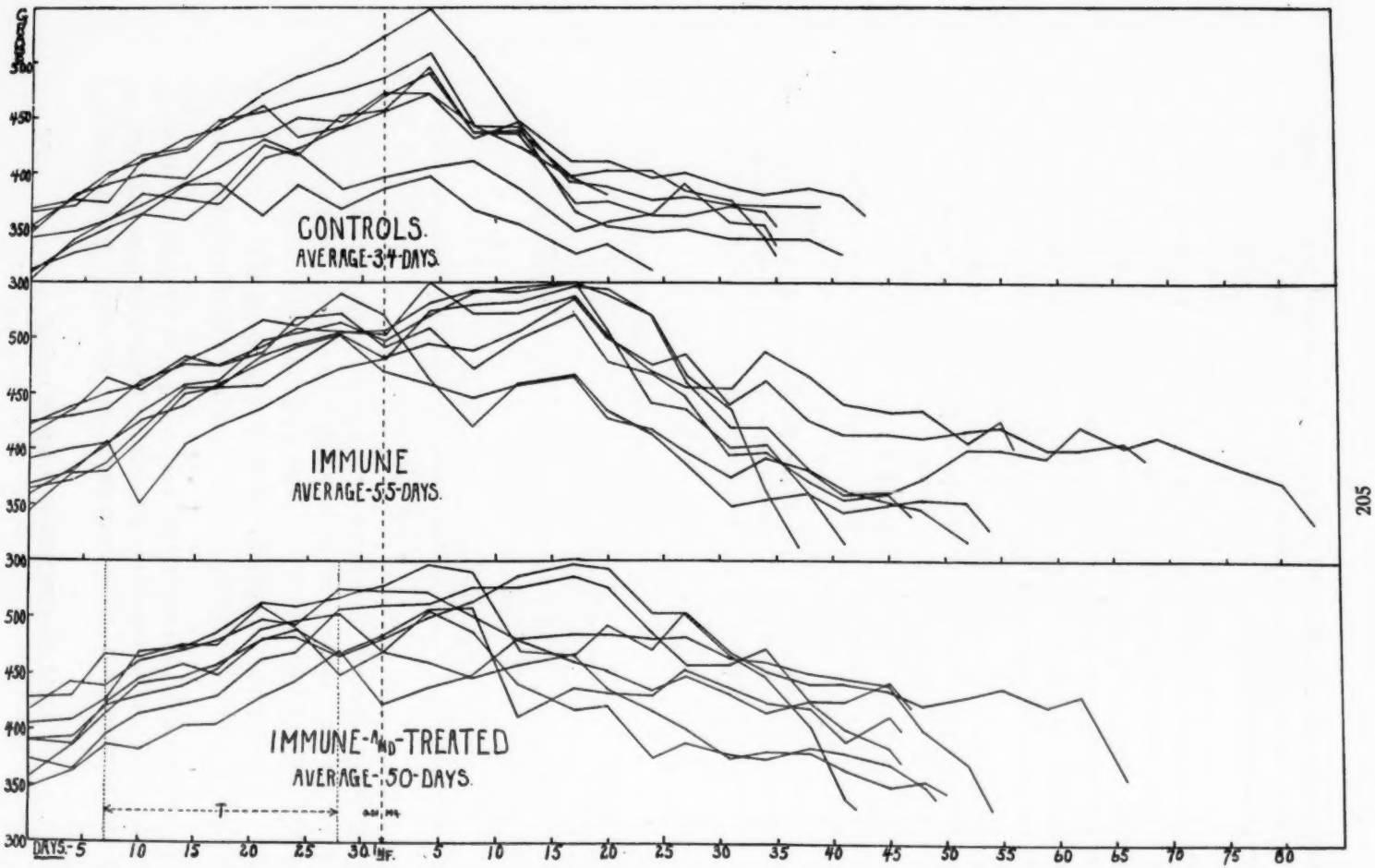

CHART 2. The effect of specific tuberculo-immunity and immunization to specific tuberculo-allergy on the duration of life of guinea pigs infected intravenously with an amount of virulent tubercle bacilli (0.01 mg.) not producing early allergic death. Specific immunization was instituted on the day the weight curves begin; "T" = immunization or desensitization to tuberculo-allergy was begun seven days later and continued to the twenty-seventh day; "INF" = infection was initiated by the intravenous injection of virulent tubercle bacilli thirty-two days after specific immunization. Death is indicated by the termination of the weight curve.

detrimental effect of the tuberculo-allergic immunization in these amounts on the tuberculosis; and this was demonstrated quite strikingly in these experiments. The weight curves also tend to verify this.

THE RECRUDESCENCE OF THE TUBERCULO-ALLERGIC SENSITIVENESS IN DESENSITIZED ANIMALS FOLLOWING INFECTION

The fluctuation and instability of the tuberculo-allergic sensitivity is a well known feature of this condition. Although our results in the foregoing experiments were rather striking in showing the significance

TABLE 1

The effect of virulent intravenous infection on the tuberculo-allergic sensitivity in tuberculo-allergic-immunized (desensitized) guinea pigs

GUINEA PIGS GIVEN A SUBCUTANEOUS INJECTION OF 1.0 MG. AVIRULENT HUMAN TUBERCLE BACILLI	RESULT OF INTRACUTANEOUS TUBERCULIN TEST WITH 1:100 NATURAL FILTRATE AND INTERVAL AFTER LAST TUBERCULO-ALLERGIC IMMUNIZING INJECTION	RESULT OF INTRACUTANEOUS TUBERCULIN TEST WITH 1:100 NATURAL FILTRATE ONE WEEK AFTER INTRAVENOUS INFECTION WITH 0.01 MG. VIRULENT HUMAN TUBERCLE BACILLI
Controls: not immunized to tuberculo-allergy....	2*	4
	1	4
	2	4
Immunized to tuberculo-allergy with 8 intravenous injections of 1 cc. 1:10 natural filtrate at six-day intervals begun one week after bacillary injection	0 (4 months)	2
	0 (4 months)	2
	0 (4 months)	1
Immunized to tuberculo-allergy at ten-day intervals with 27 injections of 1 cc. 1:4 natural filtrate subcutaneously	0 (3 days)	2
	0 (3 days)	2
	0 (3 days)	2

* The results of the readings of the tuberculin reaction are graded arbitrarily from 0 = no visible reaction to 4 = a 2 cm. erythematous oedematous reaction with central necrosis.

of the tuberculo-allergic condition in the tuberculosis picture, as segregated from the specific tuberculo-immunity, no effort was made to carry the tuberculo-allergic immunization or desensitization sufficiently far to note its complete effect on the life picture of the specific tuberculo-immune animal. That the tuberculo-allergic sensitivity does return perceptibly when virulent infection occurs, though reduced by desensitization, is depicted briefly in table 1.

The quantitative character of all these phases of the tuberculo-allergic sensitivity is attested by all these experiments. In order to note the effect, if any, produced by prolonged tuberculo-allergic immunization

(desensitization) on the general tuberculosis picture, the experiments recorded in charts 1 and 2 were repeated in essential details except that the tuberculo-allergic desensitization was initiated coincidently with the specific immunizing injection of the 1 mg. avirulent human tubercle bacilli and was continued throughout the experiment, utilizing 0.5 cc. of natural Seitz filtrate (a pure preparation obtained by growing tubercle bacilli on a simple synthetic nonprotein medium) twice a week. This is below the limit of producing any appreciable toxicity for normal animals. The results of these experiments, using 6 guinea pigs in each series and infecting intravenously with 0.01 mg. virulent human tubercle bacilli, are recorded in chart 3. The results with the 1 mg. intravenous infecting dose of virulent tubercle bacilli are not recorded here because they showed no essential significant difference from those noted in chart 1.

The duration of life of the intravenously infected *controls* in this series given only 0.01 mg. of viable virulent human tubercle bacilli was 17, 21, 22, 26, 30 and 31 days, with an average of twenty-five days; the *specific immune* guinea pigs lived 39, 40, 41, 41, 43 and 47 days, with an average life of forty-two days; and the *specific immune and tuberculo-allergic immunized* guinea pigs lived 30, 35, 49, 61, 64 and 73 days, an average duration of life of fifty-two days. The latter treated set of animals was given natural filtrate beginning on the day of specific immunization and continued throughout the experiment. The discrepancy between the different experiments in duration of life following the intravenous injection of the same amount of bacillary suspension, especially when large amounts of bacilli were injected intravenously and the suspensions were prepared at different times and from growths on different culture tubes, is not readily accounted for except that it is difficult to duplicate exactly heavy suspensions and cultures for such purposes. It is for this reason that all exact tests are planned so that the same suspension is used for infecting, especially when highly virulent strains are being used for this purpose. However, the differences are relative and never sufficiently great to overlap a difference in infecting amounts in dilutions of 1:10 usually used in graded infecting tests.

The experiment recorded in chart 3 indicates that appropriate tuberculo-allergic-immunization (desensitization) throughout the entire experimental period tends definitely to counteract the detrimental tuberculo-allergic intoxication resulting from specific tuberculo-immunity and infection with virulent tubercle bacilli. This is evident in the prolongation of life of the specific tuberculo-immune and tuberculo-allergic-im-

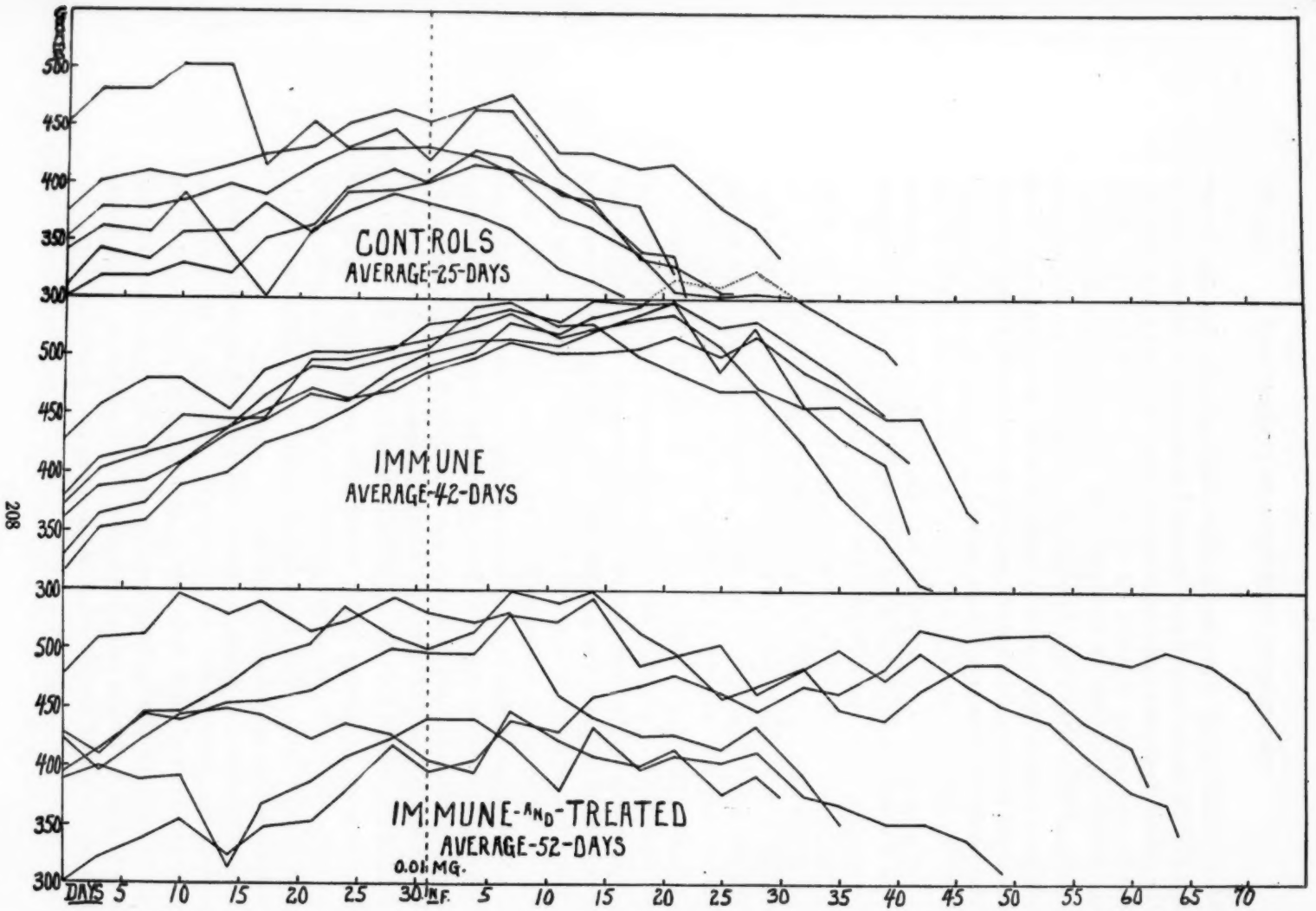

CHART 3. The effect of continued tuberculo-allergic immunization (desensitization) on the duration of life of specific tuberculo-immune guinea pigs infected intravenously with 0.01 mg. of viable virulent human tubercle bacilli. Specific tuberculo-immunization and tuberculo-allergic immunization (or desensitization) were initiated beginning with the weight curve; infection, "INF," was the intravenous injection of virulent tubercle bacilli thirty-two days later, and death is indicated by the termination of the weight curve. Note prolongation of life of specific immune animals over controls, and of specific immune and treated (tuberculo-allergic immunized) animals over the specific immunized.

munized guinea pigs which lived an average of fifty-two days in this experiment contrasted with an average of forty-two days of life for the specific tuberculo-immunized guinea pigs. In either case, the specific tuberculo-immunized guinea pigs definitely outlived those only infected which averaged only twenty-five days of life after infection in this series. It cannot be assumed, however, from this series of experiments that the duration of life of the tuberculo-allergic-immunized animals will always be greater than that of the infection controls. This is well depicted in the series recorded in chart 1 where the allergic intoxication brought to an early death some of the immune guinea pigs. Whether the effect of the treatment of guinea pigs with Seitz filtrate to immunize (or desensitize) to specific tuberculo-allergy will be beneficial or harmful depends on the infection and the amount of filtrate used. With large infecting doses (up to 0.000,1 mg. of highly virulent human tubercle bacilli), tuberculosis develops quickly; and although coincidental treatment with relatively large injections of Seitz filtrate immunizes against tuberculo-allergy, this immunity is not complete and the continued injections of large amounts of filtrate may become increasingly toxic and cause harmful or even lethal effects as the tuberculous involvement becomes greater. Thus, guinea pigs so treated may die more quickly than guinea pigs with the same initial infection but not treated. We have shown that immunization against lethal tuberculo-allergic shock in tuberculous animals is a function of tuberculous involvement. With massive involvement, protection against this lethal shock is difficult and in most cases does not occur amply.

It is thus well known that the grade of intoxication may vary with the grade of tuberculous infection. This has always been the dire problem confronting the tuberculin therapeutist since the disastrous experiences following Koch's introduction of tuberculin for the therapy of tuberculosis. Such an assumption basing tuberculin therapy in tuberculosis as an agent directly affecting the disease was entirely erroneous in the light of our present knowledge. However, the possibility of some general effect on the tuberculous organism, as has been noted previously by earlier groups of tuberculin advocates, may not have been amiss in the light of the effect of the tuberculo-allergic immunization in the experiments recorded here. However, one of the problems in practice has always been the matter of dosage to avoid detrimental intoxication versus beneficial allergic-immunization. Since this must be worked out in the light of the amount of tuberculosis infection and disease as counterpoised

tion) were initiated beginning with the weight curve; infection, "TNF," was the intravenous injection of virulent tubercle bacilli thirty-two days later, and death is indicated by the termination of the weight curve. Note prolongation of life of specific immune animals over controls, and of specific immune and treated (tuberculo-allergic immunized) animals over the specific immunized.

by intensity of tuberculo-allergic sensitivity, the ultimate practical application will have to be deferred further awaiting exact experimentation to guide such treatment instead of strict clinical observation which has been so frequently used as a guide. The strictly quantitative relations of all features of these reactions, and especially the tuberculo-allergic reactions, must be given consideration in all interpretations. These features make clinical adaptation at present undesirable without adequate gauges, which are lacking even for the investigator whose experiments are performed in a purposeful manner and to cover all the possibilities at hand, while clinical application must concern an individual alone and must be guided by means of measuring various features in this individual alone. The information thus far gained from these experiments gives us a better knowledge of the mechanism of tuberculosis in man.

SUMMARY AND CONCLUSIONS

1. Specific tuberculo-immunity prolongs the life of intravenously infected guinea pigs regardless of the amount of virulent human tubercle bacilli injected and provided tuberculo-allergic intoxication or its serious consequences do not result from this injection.

2. Appropriate immunization (desensitization) against specific tuberculo-allergy prevents acute tuberculo-allergic intoxication resulting from the intravenous injection of large infecting amounts of virulent human tubercle bacilli.

3. Appropriate prolonged immunization (desensitization) against specific tuberculo-allergy prolongs the life of specific tuberculo-immune guinea pigs following the intravenous injection of virulent human tubercle bacilli.

4. There exists a striking inverse relation between the amount of tuberculosis existing and the toxicity of the agent used to immunize against the tuberculo-allergy in spite of the development of the specific tuberculo-allergic immunity.

5. These experiments may explain the fallacy of tuberculin for treating tuberculosis when first introduced and again opens the possibility for further experimental investigation for its use under appropriate conditions to immunize (or desensitize) against specific tuberculo-allergy in tuberculosis on the basis of the biological individuality of the specific tuberculo-immunity and specific tuberculo-allergy.

SUMARIO Y CONCLUSIONES

1. La tubérculo-inmunidad específica prolonga la vida de los cobayos infectados intravenosamente, independiente de la cantidad de bacilos tuberculosos humanos virulentos inyectados, con tal que la inyección no provoque intoxicación tubérculo-alérgica o consecuencias graves debidas a ésta.

2. La immunización apropiada (desensibilización) contra la tubérculo-alergia específica, impide la producción de intoxicación tubérculo-alérgica aguda debida a la inyección intravenosa de grandes cantidades infectantes de bacilos tuberculosos humanos virulentos.

3. La immunización apropiada prolongada (desensibilización) contra la tubérculo-alergia específica protege la vida de los cobayos tubérculo-inmunes que reciben por vía venosa bacilos tuberculosos humanos virulentos.

4. Existe una notable relación inversa entre la proporción de tuberculosis presente y la toxicidad del elemento utilizado para inmunizar a la tubérculo-alergia a pesar de la producción de la específica inmunidad tubérculo-alérgica.

5. Estos experimentos pueden explicar cuán errónea fué la utilización de la tuberculina para tratar la tuberculosis cuando fué introducida por primera vez, y pone de nuevo sobre el tapete la posibilidad de ulteriores investigaciones preliminares para emplearla en condiciones apropiadas para inmunizar (o desensibilizar) contra la tubérculo-alergia específica en la tuberculosis, tomando por base la individualidad biológica de la tubérculo-inmunidad y la tubérculo-alergia específica.

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THE EFFECT OF SULFATHIAZOLE AND ALLIED COMPOUNDS ON HUMAN TUBERCLE BACILLI IN VITRO[1,2]

HARRY C. BALLON AND ALFRED GUERNON

In three previous communications (1, 2, 3), we reported that under specified conditions and in certain concentrations sulfanilamide exerts an inhibitory effect upon the growth of virulent human tubercle bacilli *in vitro*. In these experiments estimated numbers of bacilli in light suspensions were seeded upon solid media. Follis (4) who employed liquid media and large inocula failed to observe any appreciable bacteriostatic effect of either sulfanilamide or its acetyl derivative upon the growth of the tubercle bacillus (*var. hominis*). Working with liquid media Rist (5) found that 4,4′-diaminodiphenylsulfone in dilutions of 1:10,000 and 1:100,000 exerted a striking inhibitory effect upon the growth of human tubercle bacilli. Rist also reported that sulfanilamide in a concentration of 1:500 exerted complete inhibition and sulfanilamide 1:1,000 a definite retarding effect upon the growth of tubercle bacilli *in vitro*. Giroux (6) also corroborated these latter findings.

In this communication we wish to report the effect of sulfathiazole and allied compounds upon the growth of virulent human tubercle bacilli *in vitro*. We employed both solid and liquid media.

In the first series of experiments the following compounds were employed: sulfathiazole, sulfamethylthiazole, sulfanilamide, promine and sulfapyridine. In specified concentrations these drugs were added to a nutrient egg agar medium (7), and to a synthetic egg medium (8). The drugs were dissolved with the aid of heat in the liquid portion of the media. The following concentrations of the various drugs were employed: 1:1,000, 1:5,000 and 1:10,000. A suspension was prepared from an eight-day old culture. The strain employed represented the first transplant of a growth isolated from sputum. The suspension was made up in a phosphate buffer solution with a hydrogen-ion concentra-

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[2] This work was aided by a grant from the Research Department of the Winthrop Chemical Company of Canada.

tion of 8. It was centrifuged to remove the coarser clumps and was filtered through two sterile Whatman papers no. 2. A smear prepared from the filtered suspension showed on an average 10 bacilli per 100 oil immersion field. Occasional clumps of 6 to 12 bacilli were noted. The nutrient egg agar medium and Steenken and Smith's medium were inoculated with two drops of this suspension. After six weeks' incubation a very slight growth was observed in the tubes with sulfanilamide 1:1,000. The growth at six weeks was markedly retarded. There were but few colonies after ten weeks. These colonies often failed to spread and gave the appearance of abortive growths. Promine and sulfapyridine in a dilution of 1:1,000 inhibited the growth completely. At the end of ten weeks complete inhibition was observed with sulfa-

TABLE 1

Concentrations	1:1,000				1:5,000				1:10,000				Controls			
Weeks	2	3	4	6	2	3	4	6	2	3	4	6	2	3	4	6
Drugs	Growth															
A. Sulfanilamide	−	−	−	1	1	1	2	3	2	2	3	4	2	3	4	4
B. Promine	−	−	−	−	−	1	2	3	1	2	3	4	2	3	4	4
C. Sulfapyridine	−	−	−	−	−	1	1	2	1	2	2	4	2	3	4	4
D. Sulfamethylthiazole	−	−	−	−	−	−	−	−	−	−	−	−	2	3	4	4
E. Sulfathiazole	−	−	−	−	−	−	−	−	−	−	−	−	2	3	4	4

− = no growth, 1 = +, or slight growth; 2 = ++, or moderate growth; 3 = +++, or extensive growth; 4 = ++++, or very heavy growth.

At the end of ten weeks complete inhibition was observed with sulfathiazole and sulfamethylthiazole 1:10,000. The tubes with sulfanilamide 1:1,000 showed but few colonies at ten weeks.

thiazole and sulfamethylthiazole in a concentration of 1:10,000. In concentrations of 1:5,000 and 1:10,000 sulfanilamide and promine failed to exert any striking inhibitory effect at six weeks. Sulfapyridine 1:5,000 exerted a definite inhibitory effect at six weeks (table 1).

In a second series of experiments sulfathiazole was added to the synthetic egg medium in the following concentrations: 1:10,000, 1:20,000, 1:50,000 and 1:100,000. The strain recovered in the first series of experiments was employed. A suspension was prepared from a twenty-five day old culture which showed on microscopical smear 10 bacilli per 100 oil-immersion field. Small clumps of 6 to 8 organisms were present in the seeded suspension. Two drops of this suspension were inoculated upon the slants. After four weeks a slight growth was observed in the

tubes containing sulfathiazole in a concentration of 1:50,000. No growth was yet apparent with sulfathiazole 1:20,000. In the tubes containing sulfathiazole in a concentration of 1:100,000 a definite retarding effect upon the growth of the tubercle bacilli was observed at four weeks (table 2).

In a third series of experiments the actions of sulfathiazole and sulfamethylthiazole under similar conditions were again compared. These drugs in the following concentrations 1:10,000, 1:20,000, 1:50,000 and 1:100,000 were added to both the nutrient egg agar and to the synthetic egg media. On this occasion, congo-red 1:2,500 was omitted from the synthetic egg medium. A fresh strain of virulent bacilli isolated from sputum was employed in this experiment. The suspension was

TABLE 2

Concentrations	1:10,000				1:20,000				1:50,000				1:100,000				Controls			
Weeks	2	3	4	6	2	3	4	6	2	3	4	6	2	3	4	6	2	3	4	6
Drug	Growth																			
Sulfathiazole	−	−	−	−	−	−	−	−	−	−	1	2	−	1	2	4	2	3	4	4

TABLE 3

Concentrations	1:1,000	1:10,000				1:20,000				1:50,000				1:100,000				Controls			
Weeks	6	2	3	4	6	2	3	4	6	2	3	4	6	2	3	4	6	2	3	4	6
Drugs	Growth																				
Sulfanilamide	1																	2	3	4	4
Sulfathiazole		−	−	−	−	−	−	−	1	−	−	1	2	−	−	1	3	2	3	4	4
Sulfamethylthiazole		−	−	−	−	−	−	−	1		1	2	4	−	1	3	4	2	3	4	4

prepared as previously noted and showed on smear 2 to 3 bacilli per 100 oil-immersion field. Six weeks after incubation, sulfathiazole and sulfamethylthiazole 1:20,000 had completely inhibited the growth in the tubes containing the nutrient egg agar. A few scattered colonies were apparent in some of the tubes with the synthetic egg media. A slight growth was noted with sulfathiazole 1:50,000; sulfamethylthiazole in a similar concentration showed a heavier growth at six weeks. At six weeks, tubes with sulfanilamide in a concentration of 1:1,000, seeded from the above suspension, showed a very slight growth similar to that observed in the tubes in the first experiment (table 3).

In a fourth series of experiments sulfanilamide and sulfathiazole were added to flasks containing liquid medium. This medium was made

up of a neutral potato-extract-beef-infusion broth to which peptone (1.5 per cent) and glycerin (1.5 per cent) were added. Sulfanilamide was employed in a concentration of 1:1,000, while sulfathiazole was added in the following concentrations: 1:10,000, 1:20,000 and 1:50,000. The drugs were added in powder form to the media and dissolved with the aid of heat. The medium was distributed in 50 cc. portions into 250 cc. flasks. To facilitate inoculation a small sterile cork disc was allowed to float on the surface of the liquid. The medium was sterilized in the autoclave for fifteen minutes at 20 pounds pressure. Forty flasks in all were inoculated; 8 flasks for each concentration of the drug and 8 for the drug-free controls. The strain employed was that recovered in the first series of experiments and grown for six weeks on nutrient egg-agar medium. A pellicle measuring roughly 8 mm. in diameter was lifted off the slants with a loop and floated gently onto the surface of the small cork disc and fluid. After six weeks incubation growths were noted with both sulfanilamide and sulfathiazole in all concentrations. The results of this experiment were thus in principle similar to those reported by Follis (4).

In a fifth series of experiments the possible bactericidal effect of sulfathiazole was investigated. A suspension of virulent tubercle bacilli was added to a fresh clear tuberculous pleural exudate in the proportion of 10 cc. of bacillary suspension to 230 cc. of pleural fluid. The bacilli and pleural fluid were thoroughly mixed. A smear of the mixture showed microscopically one bacillus per oil-immersion field. The 240 cc. fluid-bacilli mixture was divided equally into three flasks. Sulfathiazole made up with saline (0.85 per cent) in 0.1 per cent and 0.05 per cent solutions was then added. Twenty cc. of the solutions of the drugs were added to 80 cc. of the fluid. The final concentrations of the drug were therefore 1:5,000 and 1:10,000. Saline only was added to the remaining control flasks. The contents of the flasks were thoroughly mixed and in 10 cc. amounts were transferred aseptically to tubes. After incubation for four, eight, twenty-four, forty-eight and ninety-six hours at 37°C., tubes and petri dishes with drug-free synthetic egg medium were inoculated with 0.25 cc. of a 1:50 dilution of the exudate-bacilli-drug mixtures. No appreciable bactericidal effect was observed. Insignificant minor variations in the colony count occurred, but on the average the number of colonies recovered from either the control or the sulfathiazole treated fluid was approximately the same after six weeks of incubation.

SUMMARY

Sulfathiazole and sulfamethylthiazole exert a pronounced inhibitory effect upon the growth of virulent human tubercle bacilli on solid media. Sulfapyridine, promine and sulfanilamide under similar conditions exert a less striking inhibitory effect. The inhibitory effect of sulfathiazole and sulfanilamide was not observed when a liquid medium was employed. Bactericidal tests with sulfathiazole gave negative results.

SUMARIO

El sulfatiazol y el sulfametiltiazol ejercen decidido efecto inhibidor sobre la proliferación del bacilo tuberculoso humano en medios sólidos. En condiciones semejantes, la sulfapiridina, la promina y la sulfanilamida ejercen un efecto semejante, pero menos acentuado. Ni el sulfatiazol ni la sulfanilamida ejercieron efecto inhibidor en medios líquidos. Resultaron negativos los ensayos de la facultad bactericida del sulfatiazol.

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SULFATHIAZOLE IN EXPERIMENTAL TUBERCULOSIS OF THE GUINEA PIG[1,2]

H. C. BALLON, A. GUERNON AND M. A. SIMON

Sulfathiazole exerts a more striking inhibitory effect upon the growth of virulent human tubercle bacilli *in vitro* than does sulfanilamide under similar conditions. This observation inconclusive by itself, nevertheless prompted us to investigate the effect of sulfathiazole upon the development of experimental tuberculosis in the guinea pig. Our *in vitro* experiments have been reported in the preceding paper.

Ninety-five guinea pigs were infected subcutaneously in the groin with 1 cc. of a suspension of virulent tubercle bacilli which showed on smear one bacillus per oil immersion field, previous to its being diluted one hundred times. The culture employed was from a fourteen day old transplant, isolated from sputum. The suspension appeared free of clumps. The drugs employed were administered orally in gelatin capsules. As in the case of previous experiments (1, 2, 3) the total daily amount of the drug was given in four divided doses. Differences in weight made it necessary to divide the animals into groups. The significant findings have been tabulated. In these preliminary experiments 63 guinea pigs were treated; 32 were kept as controls.

Series 1: Seventeen guinea pigs weighing, on the average, 510 g., were infected subcutaneously with 1 cc. of the bacillary suspension; 6 were kept as controls; 11 were first treated with sulfathiazole five days after infection; 5 of the treated animals died during the course of the experiment; 2 which had received 3.470 mg. of the drug died thirteen days after infection. The 2 guinea pigs which died on the nineteenth day and the twentieth day respectively had received 5.570 mg. of the drug. The fifth animal died on the twenty-eighth day. All 5 were free of macroscopical tuberculosis. The 6 guinea pigs which were sacrificed

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[2] This work was aided by a grant from the Research Department of the Winthrop Chemical Company of Canada.

thirty-five days after infection were given 510 mg. of sulfathiazole on the fifth, sixth, seventh, eighth and ninth days after infection. Two of the 6 treated guinea pigs (nos. 63 and 64) because of loss in weight received 460 mg. of the drug on the tenth, eleventh, twelfth, thirteenth, fourteenth and fifteenth days, and 360 mg. on the sixteenth day. These 2 guinea pigs were thus treated on twelve successive days. They received no sulfathiazole after the sixteenth day. The remaining 5 guinea pigs (nos. 58, 59, 60, 61 and 62) in addition to the treatments already noted, were given 460 mg. of sulfathiazole on the tenth and eleventh days after infection; 360 mg. on the twelfth, fifteenth and sixteenth days. Thus from the fifth to the sixteenth day inclusive these 5 guinea pigs received daily treatments on all but the thirteenth and fourteenth days which were rest periods. No drug was given from the seventeenth to the thirty-fifth day inclusive, when the experiment was terminated. One control animal was sacrificed on the twenty-eighth day (table 1).

Comment: Five of the 11 treated animals died during the course of the experiment. The remaining 6 guinea pigs were benefited by the drug. All treated guinea pigs which were sacrificed showed macroscopical tuberculosis in the spleen but were free of gross generalized tuberculosis. The spleens of treated animals were smaller and weighed less than those of the control animals. Similarly the tracheobronchial nodes of all treated animals were smaller than those of the controls. All treated animals lost in weight. In this connection it should be noted that all treated animals with but one exception started to regain weight nineteen days after infection. Previous to that time there had been a gradual loss in weight. None of the control animals died. Most of the controls showed a gain in weight. All control animals weighed considerably more eleven days after infection than they did at either the beginning of the experiment or when they were sacrificed. The average treatment doses in this experiment were 0.91 and 0.9 gm. per kilogram of body weight (figure 1).

Series 2: Five guinea pigs weighing on the average 440 g. were infected with 1 cc. of the suspension. Three were treated, 2 were kept as controls. All guinea pigs employed in this experiment were sacrificed thirty-five days after infection. The treated animals were given a total daily dose of only 70 mg. of sulfathiazole from the fifth to the twenty-third day and from the twenty-sixth to the thirtieth day inclusive. (See series 2, table 1.)

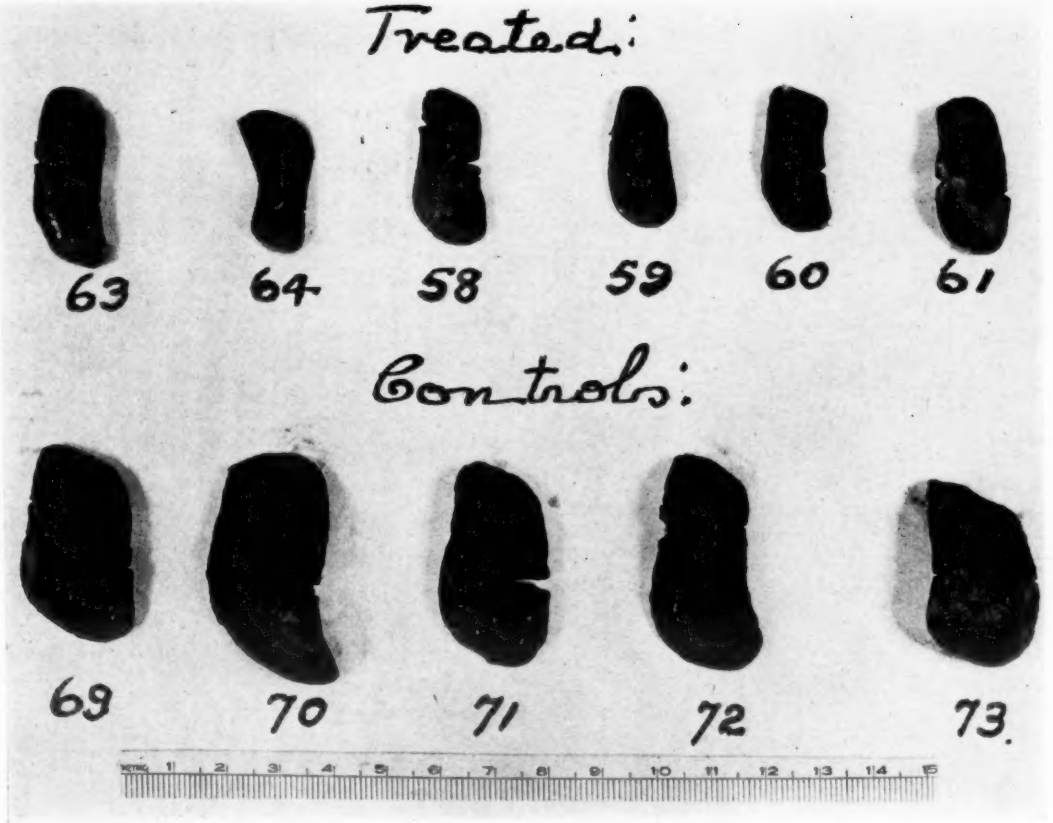

FIG. 1. Series 1. This figure shows the spleens of treated and control animals. See the text and table 1 for further details.

Comment: In this small series one of the 3 treated animals which had lost greatly in weight was benefited. The average treatment dose in this experiment was 0.16 g. per kilogram of body weight.

Series 3: Nine guinea pigs weighing on the average 470 g. were infected with 1 cc. of the bacillary suspension. Six were treated, 3 were kept

TABLE 1

	NUMBER	DAYS TREATED	TOTAL DOSE	DEGREE MACROSCOPICAL TUBERCULOSIS			WEIGHT SPLEEN	DIED	SACRIFICED
				Spleen	Liver	Lungs			
Series 1 (sulfathiazole) average weight 510 g.									
			mg.				*g.*		
Treated 5 days after infection	63	12	5,570	+	−	−	1.3		35
	64	12	5,570	+	−	−	0.8		35
	58	10	4,550	+	−	−	0.9		35
	59	10	4,550	+	−	−	0.8		35
	60	10	4,550	+	−	−	0.8		35
	61	10	4,550	++	−	−	1.3		35
	62	10	4,550	−	−	−	0.5	28	
Controls	69			++++	+++	+++	2.9		35
	70			+++	+++	+	4.9		35
	71			++++	+	++	2.7		35
	72			++++	++	+	2.4		35
	73			++++	++	+	3.2		35
	74			+++	+	+	3.8		28
Series 2 (sulfathiazole) average weight 440 g.									
Treated 5 days after infection	1	23	1,610	++++	+	+	3.0		35
	2	23	1,610	++++	+++	+	3.3		35
	3	23	1,610	++	−	−	0.9		35
Controls	4			++++	+	+	3.2		35
	5			+++	+	+	2.3		35

+ slight; ++ moderate; +++ extensive; ++++ very heavy infection.

as controls. All animals were sacrificed thirty-five days after infection. The treated animals received 70 mg. of sulfathiazole on the fifth, sixth, eighth, ninth, eleventh, twelfth, fifteenth and sixteenth days after infection. Because the above mentioned small daily doses of the drug were well tolerated and did not appear to benefit the treated animals sufficiently, as judged by the size of the regionary node, the daily dose was

increased to 280 mg. on the twentieth day after infection. Similar doses of the drug were given on the twenty-first, twenty-third, twenty-fourth, twenty-seventh, twenty-eighth, twenty-ninth and thirtieth days after infection.

TABLE 2

	NUMBER	DAYS TREATED	TOTAL DOSE	DEGREE MACROSCOPICAL TUBERCULOSIS			WEIGHT SPLEEN	DIED	SACRIFICED
				Spleen	Liver	Lungs			
Series 3 (sulfathiazole) average weight 470 g.									
			mg.				*g.*		
Treated 5 days after infection	49	16	2,800	+++	−	−	1.3		35
	50	16	2,800	++	−	+	1.8		35
	51	16	2,800	++++	+++	+	3.4		35
	52	16	2,800	+++	+	++	1.6		35
	53	16	2,800	++	+	+	1.2		35
	54	16	2,800	+++	+++	++	2.1		35
Controls	55			++++	++	++	3.2		35
	56			++++	+++	+	5.2		35
	57			++++	+++	+++	3.3		35
Series 4 (sulfathiazole) average weight 315 g.									
Treated 5 days after infection	6	19	2,660	++	+	−	1.6		35
	7	19	2,660	+++	++++	++	3.0		35
	8	19	2,660	+	−	−	1.3		35
	9	19	2,660	+++	+++	++	2.5		35
	10	19	2,660	++	+	+	2.0		35
	11	19	2,660	++	++	+	1.7		35
	12	17	2,380	−	−	+	1.4		35
	13	17	2,380	+++	−	−	2.3		35
Controls	16			+++	++	++	2.6		35
	17			++	++	+	2.2		35
	18			++++	++++	++	2.3		35
	19			++++	++	+	2.6		35
	20			+++	+	++	3.3		35

Comment: Despite the fact that treated animals received very little sulfathiazole during the first three weeks after infection, 3 of the 6 treated animals were benefited. The average treatment dose in this experiment was 0.37 g. per kilogram of body weight (table 2).

Series 4: Fifteen guinea pigs weighing on the average 315 g. were infected subcutaneously with 1 cc. of the suspension. Ten were treated,

5 were kept as controls. Two of the treated animals (nos. 14 and 15) were purposely sacrificed thirty days after infection. Both had taken 2,380 mg. of the drug; both were free of macroscopical tuberculosis.

The remaining 8 treated animals received 140 mg. of sulfathiazole in four equally divided doses on and from the fifth to the eighteenth day after infection and on the twenty-first, twenty-second, twenty-third, twenty-seventh and twenty-eighth days after infection. The intervening days were rest periods when no drug was given. (See Series 4, table 2.)

Comment: Five of the 8 treated guinea pigs which were sacrificed thirty-five days after infection were appreciably benefited by the drug. The 2 treated guinea pigs which were sacrificed thirty days after infection were also benefited. They have not been included in the final results. Attention is again drawn to the small daily dose of the drug which was given to the treated guinea pigs in this experiment. The average treatment dose in this experiment was 0.44 g. per kilogram of body weight.

Series 5: Eight guinea pigs weighing on the average 525 g. were infected with 1 cc. of the suspension. Five were treated, 3 were kept as controls. One of the treated animals died twenty days after infection. It had taken 2,240 mg. of the drug. It was free of macroscopical tuberculosis. The 4 treated animals which were sacrificed thirty-five days after infection received 280 mg. of sulfathiazole on the fifth, sixth, eighth, ninth, eleventh, twelfth, fifteenth, sixteenth, twenty-seventh and twenty-eighth days after infection (table 3).

Comment: Three of the treated animals in this experiment were benefited by the drug. One guinea pig was not benefited, one died twenty days after infection. The average treatment dose in this experiment was 0.53 g. per kilogram of body weight.

Series 6: Thirteen guinea pigs weighing on the average 625 g. were infected with 1 cc. of the suspension. Seven were treated, 6 were kept as controls. The treated animals received 610 mg. of sulfathiazole on the fifth, sixth, eighth, ninth, eleventh and twelfth days after infection. On the fifteenth and sixteenth days after infection they received 560 mg. of the drug. (See Series 6, table 3.)

Comment: One treated guinea pig died eighteen days after infection. One control animal died thirty-two days after infection. It showed generalized tuberculosis. The spleen in this instance measured 42 by

17 mm. Three of the treated animals in this series were regarded as benefited by the drug. Only eight daily treatments were given in this experiment. This together with the fact that the treatments were not given on successive days may account for the less favorable results as compared with those obtained in series 1. The average daily treatment dose in series 6 was 0.95 g. per kilogram of body weight.

TABLE 3

	NUMBER	DAYS TREATED	TOTAL DOSE	DEGREE MACROSCOPICAL TUBERCULOSIS			WEIGHT SPLEEN	DIED	SACRIFICED
				Spleen	Liver	Lungs	Spleen		
Series 5 (sulfathiazole) average weight 525 g.									
			mg.				*mm.*	*g.*	
Treated 5 days after infection	75	10	2,800	+	−	+	31 x 13	1.1	35
	76	10	2,800	++	−	−	30 x 14	1.2	35
	77	10	2,800	+	−	+	29 x 14	1.2	35
	78	10	2,800	+++	+	+	43 x 21	3.8	35
Controls	80			++++	+	+	47 x 20	3.3	35
	81			++++	++	+++	44 x 21	3.5	35
	82			+++	+	++	48 x 21	2.7	35
Series 6 (sulfathiazole) average weight 625 g.									
Treated 5 days after infection	83	8	4,780	++	−	+	35 x 20	2.4	35
	84	8	4,780	+++	+	+	42 x 20	3.5	35
	85	8	4,780	+	+	+	31 x 15	1.6	35
	86	8	4,780	+++	+	++	45 x 22	3.2	35
	87	8	4,780	+	−	−	33 x 17	1.8	35
	88	8	4,780	+++	+	+	41 x 23	3.3	35
Controls	90			++++	++	++	64 x 32	8.4	35
	91			+++	+	+	41 x 21	2.9	35
	92			+++	++	++	44 x 21	3.2	35
	93			++++	+	+	47 x 20	3.2	35
	94			+++	+	+	40 x 18	1.7	35

Series 7: Twenty-eight guinea pigs weighing on the average 375 g. were infected with 1 cc. of the suspension. Five were treated with sulfamethylthiazole, 5 with sulfathiazole, 6 with sulfapyridine and 5 with sulfanilamide. Seven guinea pigs were kept as controls. All treated animals received the drug on the same days.

The 5 animals which were given sulfamethylthiazole received 450 mg. of the drug on the fifth, sixth, eighth, ninth, eleventh and twelfth days

after infection. One treated animal died on the thirteenth day. The remaining 4 animals received 350 mg. on the fifteenth and sixteenth days. Another treated animal died on the sixteenth day. The 3 remaining animals received 350 mg. of sulfamethylthiazole on the twenty-second, twenty-third, twenty-seventh and twenty-eighth days and were sacrificed on the thirty-fifth day after infection. The average treatment dose was thus 0.97 g. per kilogram of body weight.

Five guinea pigs received 460 mg. of sulfathiazole on the fifth, sixth, eighth, ninth, eleventh and twelfth days; and 360 mg. on the fifteenth, sixteenth, twenty-second and twenty-third days after infection. Two of the 5 treated animals (nos. 21 and 24) did not receive any sulfathiazole on the twenty-seventh and twenty-eighth days when the other 3 treated guinea pigs received 360 mg. of the drug. The average treatment dose was 1.1 g. per kilogram of body weight.

Six guinea pigs were given 450 mg. of sulfapyridine on the fifth, sixth, eighth, ninth, eleventh and twelfth days after infection. One treated animal died on the thirteenth day, another on the fourteenth day. The remaining animals received 340 mg. of sulfapyridine on the fifteenth and sixteenth days. A third animal died on the eighteenth day. The 3 remaining animals were given 340 mg. of the drug on the twenty-second, twenty-third, twenty-seventh and twenty-eighth days and were sacrificed on the thirty-fifth day. The average treatment dose for this group was 1.08 g. per kilogram of body weight.

Five animals were given 420 mg. of sulfanilamide on the fifth, sixth, eighth, ninth, eleventh and twelfth days. On the fifteenth and sixteenth days 315 mg. of sulfanilamide were given. Two of the treated animals received 315 mg. of the drug on the twenty-second, twenty-third, twenty-seventh and twenty-eighth days. One animal did not receive any drug after the sixteenth day. Two did not receive any drug after the twenty-third day; one of these animals died on the twenty-fourth day. The average treatment dose for this group was 1 g. per kilogram of body weight (table 4).

Comment: Because of slight variations in the treatment dose the results of this experiment do not permit of comparison. Three of the 5 guinea pigs treated with sulfamethylthiazole were benefited; 2 died during the course of the experiment.

Three of the 5 animals treated with sulfathiazole were benefited; all 5 were sacrificed thirty-five days after infection.

Two of the 6 animals treated with sulfapyridine were benefited; 3 of

the animals treated with sulfapyridine died during the course of the experiment.

One of the animals treated with sulfanilamide was slightly benefited; 3 were not benefited, one died. On the basis of past experiences we are

TABLE 4

	NUMBER	DAYS TREATED	TOTAL DOSE	DEGREE MACROSCOPICAL TUBERCULOSIS			WEIGHT SPLEEN	DIED	SACRIFICED
				Spleen	Liver	Lungs			
Series 7, average weight 375 g.									
			mg.				g.		
Treated with sulfamethylthiazole 5 days after infection	37	12	4,650	+	−	−	1.1		35
	38	12	4,650	+	−	−	1.1		35
	39	12	4,650	+	−	−	1.0		35
Treated with sulfathiazole 5 days after infection	22	12	4,920	++	+	−	0.7		35
	23	12	4,920	+	−	−	0.8		35
	25	12	4,920	±	−	+	0.8		35
	21	10	4,200	+++	+	+	1.4		35
	24	10	4,200	+++	+++	++	1.8		35
Treated with sulfapyridine 5 days after infection	26	12	4,740	++	++	+	1.2		35
	28	12	4,740	+	−	+	1.0		35
	27	10	4,060	+++	++	+++	2.4		35
Treated with sulfanilamide 5 days after infection	32	12	4,410	+++	−	++	1.7		35
	33	12	4,410	++	+	+	1.2		35
	34	10	3,840	+++	+	+	1.8		35
	35	8	3,150	+++	+	++	2.9		35
Controls	42			++++	+	+	3.0		35
	43			++++	++++	++++	3.5		35
	44			++++	+	++	4.6		35
	45			++++	+	+	3.2		35
	46			++++	+++	+	4.0		35
	47			++	+	+	1.5		35
	48			++++	++++	++	3.7		35

of the opinion that more and heavier treatments than were given are necessary in order to obtain an inhibitory effect with sulfanilamide.

HISTOLOGICAL EXAMINATION

The spleens, livers, lungs, kidneys and inguinal lymph nodes draining the site of original infection of treated and control animals of series

3, 5, 6 and 7 were examined microscopically. This examination was completely objective since the specimens had been renumbered. As nearly as possible, complete sagittal sections of spleen, kidney and liver were taken; all sections of lung consisted of the entire right lower lobe.

Microscopically, no differences in qualitative reactions could be detected between control and treated animals. In general, the more extensive the tuberculosis, the greater the tendency toward necrosis regardless of treatment. No fibrosis or other evidences of healing could be identified in any organs of treated or control animals.

Only quantitative differences could be noted between various animals. This objective, microscopical and quantitative grading closely paralleled the macroscopical grading.

Since draining lymph nodes of the original site of injection are readily infected secondarily, the size of these nodes is not the most suitable yardstick. As in the last group of experiments reported by us (3), the best single indicator of the extent of tuberculosis is the size of the spleen. In only 2 of all the control animals was the spleen as small as any treated animal of a particular series. In general, the spleens of any group of treated animals were smaller in size and weight (see figure 1) than the controls within such a group. The guinea pigs in each series, both treated and control, were selected to avoid large differences in weight or size.

The amount of tuberculosis in the other organs examined roughly paralleled that found in the spleens of the same animals with the exception of the kidneys which are relatively infrequently affected. In none of the kidney sections of the treated animals was any crystalline deposit or dilatation of collecting tubules noted. A number of treated animals showed a mild, chronic pyelitis but this condition was also noted in a number of control animals; all without renal tuberculosis. In none of the treated animals was there microscopical change which could be attributed to the effects of the drugs used.

DISCUSSION

In the first six series of experiments 67 animals were used; 42 were treated, 25 were kept as controls. Seven of the treated animals died during the course of the experiment. All were free of macroscopical tuberculosis. Only one animal (no. 62) of this group is included in the final analysis. One control animal (no. 74) was sacrificed twenty-eight days after infection. All control animals with the one exception noted

above were sacrificed at the conclusion of the experiment, thirty-five days after infection. Two of the treated animals (nos. 13 and 14) not referred to in the tables were sacrificed thirty days after infection. They were free of macroscopical tuberculosis.

If we now consider the remaining 34 animals treated with sulfathiazole which fulfilled the requirements of the experiment, then it may be stated that 22 were benefited. We regard this result as encouraging since but few of the treated animals can be said to have received large doses of sulfathiazole. The beneficial results obtained appear to depend upon the size of the treatment dose and upon the time the treatments were given. These facts are suggested by the analysis of the results of individual experiments.

Seven adequately treated animals in series 1 were all benefited by the administration of sulfathiazole. In this experiment the average treatment dose was 0.9 g. per kilogram of body weight.

In series 2 only one of the 3 treated animals was benefited. The average treatment dose in this experiment was only 0.16 g. per kilogram of body weight.

Three of the 6 treated animals in series 3 benefited from the treatment which they received. The average daily treatment dose in this experiment was 0.37 g. per kilogram of body weight.

Five of the 8 treated animals in series 4 were benefited by the drug. The average daily treatment dose in this instance was 0.44 g. per kilogram of body weight.

In series 5, 3 of the 4 treated animals were benefited. The average daily dose in this experiment was 0.53 g. per kilogram of body weight.

Only 3 of the 6 treated animals in series 6 were benefited by the drug. The average daily treatment dose in this experiment was 0.95 g. per kilogram of body weight. One should have expected more favorable results in this series. The animals in series 1 received more treatments than did those in series 6. The animals in series 6 weighed on the average more than did those in series 1. The daily dose was larger in the former, the average treatment dose about the same.

The results which we obtained with sulfathiazole thus far do not permit of direct comparison with those obtained with sulfanilamide and reported by us elsewhere. From our experiments it would appear that perhaps less sulfathiazole and fewer treatments with sulfathiazole are necessary in order to obtain the same inhibitory effect noted with sulfanilamide. More experiments are however necessary to prove these

points. The preliminary experiments with sulfamethylthiazole and sulfapyridine suggest that they may exert an inhibitory effect, particularly the former.

SUMMARY

In adequate doses sulfathiazole appears to exert some inhibitory effect upon the development of experimental tuberculosis in the guinea pig. These results do not permit of clinical application.

SUMARIO

A dosis adecuadas, el sulfatiazol parece ejercer algún efecto inhibidor sobre la evolución de la tuberculosis experimental en el cobayo. Los resultados obtenidos no permiten la aplicación clínica del medicamento.

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BOOKS

JACOB SEGAL: *Diseases of the Respiratory Tract. With Foreword by Harry Wessler. Pp. ix + 172, Oxford University Press, New York, 1941, cloth, $2.00.*

By LEWIS J. MOORMAN

In this small volume of 172 pages, we find a valuable compendium of the respiratory diseases. In this field, rapid development in diagnostic and therapeutic procedures keeps the medical student and the alert doctor constantly on the look-out for additional knowledge.

With the perennial prevalence of respiratory diseases and the seasonal accentuation of their importance constantly in mind, such a reference book should become the pocket companion of the medical student, the intern and the busy doctor. Those in need of immediate information and those who have read and forgotten, or who are too busy to read in great detail, will find in this handy volume the essential facts brought up-to-date.

On the other hand, this outline should not be considered as merely a short cut to knowledge. The author admits that isolated facts often suffer for want of amplification and proper association with related facts.

The following quotation from the Preface should serve as a guide for every one who makes use of this valuable outline. "One may read and absorb the descriptive text of a certain disease, yet fail to visualize the essential points clearly. The detailed exposition when read and reread attentively will leave a good general impression of the subject, but is apt to blur the salient and sequential delineation. An outline is calculated to help the reader systematize his thoughts on the subject matter he has read about extensively and repeatedly in the textbook. It should be helpful to focus attention on essentials, and recall to memory the details in their proper proportion. I hope that the outline here presented will fulfill the aforementioned requirements."

The subject matter is presented in seven sections or chapters, with the following titles: Diseases of the Nasal Cavities; Diseases of the Pharynx; Diseases of the Lymphatic Structures of the Pharynx; Diseases of the Larynx; Diseases of Trachea and Bronchi; Diseases of the Lungs; Diseases of the Pleura; Bibliography; Index.

A careful perusal of the brief but comprehensive text shows that the author, through a lucid style, has succeeded in giving an accurate statement of facts in very few words. While the reader may occasionally regret the brevity necessary in such a book and note the omission of certain conditions, he must marvel at the store of knowledge made available in so few pages.

ARTHUR J. AMOR: *An X-ray Atlas of Silicosis. With translation of the legends into French by Robert E. Horne, and with Foreword by Sir Wilson Jameson. Pp. xii + 206, with 72 plates, The Williams & Wilkins Company, Baltimore, 1941, cloth, $8.00.*

By LEROY U. GARDNER

The purpose as defined in the preface "is to set out the essential radiological features of silicosis for senior students, examining surgeons under the Factory Acts and others whose work is intimately connected with industrial diseases." The author has supplemented his own material from the coal miners of South Wales with that from other English industries to furnish illustrations of most of the major variants of silicosis.

Five short introductory chapters deal with aetiology, pathology, radiological examination of the lungs, clinical manifestations and prognosis. The treatment is probably adequate for the general medical audience although the subject of aetiology might profitably be treated in more detail. It is regretted that a writer who must have had wide experience in the estimation of disability should dismiss the subject with one short paragraph. Case histories appended to the illustrations demonstrate the severity of pulmonary change which can exist with only partial disability. The nomenclature may prove confusing to American readers as he speaks of both infective silicosis, the condition in which an element of latent infection alters localization of the dust reaction, and of silico-tuberculosis the one in which the infection ultimately becomes active.

The plates are accompanied by a brief résumé of the occupational and medical histories, clinical findings, radiographic appearances and diagnosis both in English and in French. The cases are arranged in groups to illustrate normal and nonspecific dust reactions, typical silicotic reactions, the development and distribution of conglomerate lesions, silico-tuberculosis, acute silicosis, silicosis in various industries, complications and differential diagnosis. There are few plates, not particularly well done, to illustrate pathological specimens and 6 text figures for histo-pathology. The plates are adequate to depict all gross roentgenographic patterns and some of the finer ones. In some, essential details are lacking that would have been apparent in a transparency.

The author recognizes that coal miners, his major source of material, characteristically develop a modified type of silicosis and for that reason he has introduced examples of the disease from other industries. He does not make it clear, however, that the conglomerate forms of reaction, whose evolution he illustrates in detail, are unduly common in anthraco-silicosis. There is also a tendency to stress minor variants as characteristic of the disease in particular industries. For example, he feels that "eggshell calcification" of lymph

nodes is peculiar to slate workers but the reviewer has observed several instances of this condition where there had been no exposure to slate dust.

Conforming to American practice the author considers "linear changes" in the chest roentgenogram as nonspecific conditions which may or may not be due to silica dust. He states that they are often caused by mixtures of quartz and other minerals. As a forerunner of specific nodular shadows, however, he introduces a new roentgenographic category designated as "reticular" shadows. These he believes are due to perilymphatic reaction in the interlobular septa, "a thickening which will eventually develop into a silicotic nodule." Histologically the lungs of coal miners do show reaction in this location, but most of the nodules do not develop within them. He also mentions another type of reticulation representing a predominance of interstitial fibrosis, most common in the middle and lower thirds of the lung fields. However, this term is not used to describe two cases of asbestosis illustrated under differential diagnosis. To the reviewer these uses of the term, reticulation, are confusing and in this country are apt to cause difficulties as a few authors have already employed the same designation to describe the pneumoconiosis produced by talc and some other silicates.

The volume should be helpful to any physician unfamiliar with the different roentgenographic manifestations of silicosis. He should bear in mind, however, that any of these patterns may be produced in any industry with a silica hazard and that individual cases exhibit nothing characteristic of exposure in a pottery, an iron mine, a coal mine or a sandblast cabinet.

LUIS SAYÉ: *Doctrina y práctica de la profilaxis de la tuberculosis. Pp. 355, with numerous tables, charts and illustrations, Editorial sudamericana, S. A., Buenos Aires, cloth.*

By HOWARD B. SHOOKHOFF

In this work, Professor Sayé presents an up-to-date survey of the results of the application of present-day preventive measures in the field of tuberculosis. He points out the limitations of these techniques and discusses at length two methods which he feels should go a long way toward overcoming these limitations, namely, the radiophotography technique of Abreu and vaccination with tubercle bacilli. The book is of special interest in that it presents a thorough study of the results of vaccination analyzed by one who is something of an enthusiast.

Part I presents a broad epidemiological survey. The development of an epidemic wave beginning in England and Germany in the seventeenth century and spreading slowly north, east and south in Europe and still persisting at

present is pointed out. Similar epidemic phases are noted in North America in the nineteenth century and in South America and Asia in the twentieth century. These are related to gathering of large masses of population under unhygienic conditions. The influence of population density, racial factors and general socio-economic levels on the character of the epidemic spread of tuberculosis is discussed and related to statistics gathered from various parts of South America.

The results of surveys made by the author and his collaborators in Lima, Montevideo, Santiago de Chile and Buenos Aires are presented. These show a general parallel between morbidity and mortality on the one hand and the number of occult cases discovered by routine examinations on the others. Certain differences between the cities are discussed and explained on racial and socio-economic grounds.

Part II constitutes the largest portion of the book. It presents a strong case for the efficacy of BCG vaccine in a study of almost 1,200 children, approximately half of whom were vaccinated. For purposes of study they were divided into those exposed at birth, those exposed after two months of age and those not exposed. Clinical, radiographic and tuberculin studies were made independently of one another. The over-all results show 30 per cent of active disease in the nonvaccinated as opposed to 4 per cent in the vaccinated. Comparison of cases of both types exposed in the family group presents further cogent evidence for the effectiveness of the procedure. Various differences in allergy and in the mode of handling infection in the vaccinated as compared with the nonvaccinated are pointed out as evidence of increased resistance. These results are comparable to favorable results reported from other parts of the world.

A comparison of the results of different methods of vaccination—oral, multiple puncture and intracutaneous—is made. In general, a greater degree of resistance and a lesser degree of allergy is noted on exposure in the vaccinated. The best method of vaccination has yet to be determined. The author believes in repeated revaccination which he feels improves resistance without altering allergy. He advises revaccination during recovery from active disease.

Part III discusses the usefulness of radiophotography. It is excellent for group prophylaxis for it reveals especially well open and early exudative lesions. Its application to individual cases must be supplemented by clinical data and X-ray films. The technical reasons for the usefulness and limitations of radiophotography are presented with illustrative cases.

Part IV discusses the historical development of preventive technique in tuberculosis and the effectiveness of present-day preventive methods in reducing morbidity and mortality. Close observation shows that the rate of descent of the curve of tuberculous infection has decreased in the past ten years. The results are falling far short of the complete eradication of the disease. This

has occurred because present methods fail to take account of many carriers. Preclinical cases, arrested cases, asymptomatic primary infections, all give off bacilli. On the one hand, there is a reservoir of infection in preclinical and subclinical cases, and on the other, a reservoir due to failure of real lasting cure in the majority of open cases. To a great extent, present measures merely delay the time of onset of infection. We must add to our armamentarium BCG vaccination and radiophotography. The following program is proposed:

1: Thorough investigation to understand the distribution and character of the infection and the needs of those affected.
2: Hospital, sanatorium and dispensary facilities in accordance with epidemiological findings.
3: Vaccination of all healthy tuberculin-negative individuals.
4: Systematic periodic group examinations.
5: Socio-economic betterment.

The initial efforts should be directed at the population groups most in need, as shown by surveys. For example, in areas undergoing massive tuberculization, the newborns need vaccination. In more endemic areas, young women should be the first submitted to group health examinations. There is evidence that this scheme will produce results even without improvement in economic status, but eventually a limit of success is reached, depending upon the economic status of the group.

GEORG SIMON: *Diagnostik und Klinik der Lungentuberkulose des Kindesalters. Pp. 75, with 44 illustrations, 1940, Ferdinand Enke Verlag, Stuttgart, paper, RM 5.*

By EDITH M. LINCOLN

This monograph on tuberculosis of the lungs in children is an excellent exposition by a man thoroughly acquainted with the subject. Throughout the book the concept of tuberculosis of the lungs as an entity is emphasized. Stress is laid on the great variation of the clinical pictures and the marked tendency to exacerbations even when the ultimate prognosis is good. The development of chronic pulmonary tuberculosis in the child and adolescent as a sequel to the childhood disease is illustrated by many examples. Extrapulmonary complications are not discussed, except for a chapter on tuberculous meningitis which for some reason is included. The bibliography omits many names associated with the literature on tuberculosis in children. The monograph suffers greatly because of the very poor schematic drawings which are the only illustrations and supposedly represent X-ray findings.

1000 Questions and Answers on T.B. Edited by FRED H. HEISE. *Pp. vi + 235, National Tuberculosis Association, New York, 1941, cardboard, $1.00.*

By MAX PINNER

A book that presents information for patients should be scrutinized as to the reliability, completeness and suitability of its content and in regard to its understandability for and appeal to patients.

To take the second point up first: I have given Doctor Heise's book to some of our Sanatorium patients and asked them for their opinion. Here are some representative sentences: "There is a great deal of repetition and I do not think it is a book to be read from cover to cover, but I believe it is an excellent book to be used for reference by tuberculosis patients. . . ." "The book covers practically all of the questions that most of the patients discuss among themselves." "Very few medical terms are used which makes it easy for the patient to understand." "The book is most helpful to the tuberculosis patient, especially that patient who is new to the disease. . . ." ". . . easily comprehensible to the most uninformed lay person." ". . . it fulfills its purpose and stands as a 'must' on the list of every tuberculosis patient." These scattered citations prove that the patient is well pleased, even enthusiastic.

From the point of view of the physician—whose work can be greatly lightened by a judicious distribution of Doctor Heise's book—there is but little to add. The information is solid and reliable and carefully evades, as a rule, controversial subjects. It contains but few statements with which almost every physician would not agree. Some such exceptions may be mentioned.

The differentiation that is made between radiation from the sun and that from quartz lamps (page 131) is not well supported by facts. Either radiation may be harmful, it is not a question of wave-length (within the limits of the two sources) but of quantity.

The importance of heredity (page 3) is probably far underrated.

The "time of life" when "most first infection" occurs (answer: childhood) should have been subject to revision in 1941.

In some answers on infectivity, too much confidence seems to be placed on the results of negative sputum examinations. Is it wise to assure a patient that he is not contagious because his sputum has turned negative and remained so for several months? With every further step in the improvement of bacteriological methods, true sputum conversions become fewer. It is probably justified to instruct many patients that—regardless of sputum findings—they must behave *as if* they had positive sputum.

A certain percentage of questions are so specified that the answers to them are hardly of interest to anyone but the original questioner. It would be desirable in a future edition to shape all such questions in such a way that they would provide more general applicability.

But, after all minor criticisms have been voiced, the fact remains that Doctor Heise's book is most useful and it is to be hoped that it will find broadest distribution.

H. W. HETHERINGTON AND FANNIE ESHLEMAN: *Nursing in Prevention and Control of Tuberculosis. Pp. xix + 316, with numerous photographs and charts, G. P. Putnam's Sons, New York, 1941, fabrikoid, $3.00.*

By H. R. NAYER

The nurse plays a rôle of the highest importance in the field of tuberculosis. Adequate nursing in this disease provides not only for the physical comfort of the patient but also recognizes the importance of mental and emotional factors. The tuberculosis nurse must assume definite responsibilities in the public health handling of the disease. The visiting nurse frequently builds up a close association with the family and she is, therefore, able to play a large part in the education of the family group. The nurse is also called upon to aid in the postsanatorium care and rehabilitation of the patient.

These functions of the nurse in chronic disease in general and tuberculosis in particular require a general viewpoint which is, all too frequently, not familiar to the student nurse graduating from the general hospital. Her experience with the disease is often limited and casual and her brief contact with the patient, before he is transferred to a tuberculosis institution, offers little opportunity for the development of an adequate understanding of the inherent major problems.

It is true that nursing schools offer a short course in tuberculosis as part of the general course. For those who are interested, elective courses and practical experience are often available. The first series of lectures must, therefore, cope with a big problem in an all too brief period of time. For those with some experience in teaching tuberculosis to nurses, the importance of a good textbook, as an aid in amplifying the lecture material, can hardly be overemphasized.

In this respect, the text under discussion fills a real need most adequately. The authors are both associated with the Henry Phipps Institute and have obviously had a rich experience in the field. The presentation is clear and basic and includes every aspect of the subject. The technical aspects of nursing in tuberculosis are well covered. Even more important is the excellent presentation of the aspects peculiar to tuberculosis, an understanding of which is essential for the development of a correct approach to the disease. These include the public health importance of the disease, the rôle of social and economic factors, the importance of the family unit and rehabilitation.

A brief review of the anatomy of the lungs would, I believe, enhance the value of the book as a text. In view of the fact that the National Tuberculosis Association has recommended that the terms "childhood infection" and "adult infection" be discarded, their inclusion may serve to confuse the student. Finally, certain physiological concepts which often puzzle the elementary student are not adequately explained. For example, the negativity of intrapleural pressure is mentioned in a part of a sentence which does not clarify the mechanisms involved.

This book will be a valuable addition to any nursing library. It can be recommended, not only to elementary students; it can be read with great profit by all nurses and especially by those who are in any way connected with nursing in tuberculosis. A reading of this book will serve, not only to increase the nurse's education, but will give her a clear picture of the important rôle she can play in the "all out" fight against the disease.

FRIEDRICH ELLINGER: *The Biologic Fundamentals of Radiation Therapy. English translation by Reuben Gross. Pp. xvi + 360, with 79 illustrations, 1941, Elsevier Publishing Company, Inc., New York, Distributors: Nordemann Publishing Company, Inc., cloth, $5.00.*

By K. HARPUDER

Within the small space of some 330 pages, Doctor Ellinger has given us a concise but thorough review of radiation therapy, covering the fields of X-ray, corpuscular rays, ultraviolet radiation, visible rays and infrared rays. The outstanding feature of the book is an attempt, very successful as a whole, to rationalize radiation therapy and to connect its various applications with its physiological and experimental effects. Experimental literature is, therefore, widely quoted and the book is, especially in this respect, an unusually rich source of information. The value of the book is further enhanced by the sound critical viewpoints of the author, possible only in a man who has himself spent years in successful experimentation. The physics of radiation therapy and many problems of radiation practice are only briefly touched, although always clearly and concisely treated. Ultraviolet therapy of tuberculosis is taken up in seven pages with a brief historical review and a great deal of critical and practical information.

The translation of the text from the German is smooth and readable. A number of good illustrations and especially a bibliography of 1,100 numbers will be appreciated by the student.

The book can be highly recommended to the radiation specialist as well as to the physician with a deeper interest in radiation therapy.

JAMES T. CULBERTSON: *Immunity against Animal Parasites. Pp. x + 274, New York, Columbia University Press, 1941, cloth, $3.50.*

By H. J. CORPER

In presenting this textbook, it was hoped to acquaint beginners with the fundamental principles of the study of immunity to the parasitic forms as now understood. It was also intended to give the more experienced a thorough orientation and collation of the heterogeneous and voluminous recent literature dealing with immunity in parasitic infection. Therefore, the available material is treated in a manner deemed most useful to the beginning student, the trained investigator and the practicing physician or veterinarian. Personal concepts and theories, of the author and others, are held to a minimum, being wholly avoided unless supported by experimental data. The book presupposes a knowledge of both parasitology and immunology; no elementary delineation of either parasitic life history or of general principles of immunity is given. Aside from a short introduction, the book is presented in three parts: (*1*) Natural Resistance and Acquired Immunity; (*2*) Immunity in Specific Diseases; and (*3*) Applied Immunology. A running reference is carried through the book at the bottom of each page and an eighteen-page index completes the volume. The present book refers to Taliaferro's monograph of 1929 for literature antedating that time and covers mainly the last twelve years. The host-parasite relation is pointed to again as a protection of one from the other, with each carrying on its essential life processes in spite of the presence of the other. Natural resistance is considered to be one exerted equally and with similar effect upon a variety of parasites. It may not always be present from birth but can be developed only after the host has grown older. To some parasites, the host never becomes naturally resistant and remains susceptible to infection on initial exposure so long as it lives. As a result of first exposure, however, forces distinct from those responsible for natural resistance are set in motion by the host which generally enable it to check the progress of the parasite and sometimes cause the parasite to leave the host. Usually these forces are less powerful than those which account for natural resistance, but they are at the same time more specific in action upon the parasites. Such specific forces remain with the host so that they may be called forth again when the same parasite threatens. Two observations, the first clear demonstration of an acquired immunity in Texas fever of cattle by Smith and Kilbourne in 1893 and in the rat after initial infection with *Trypanosoma Lewisi* in 1899, represented practically all that was known of specific immunity to animal parasites at the dawn of the twentieth century. The first three decades of this century were chiefly concerned with the development of tests for the diagnosis of various infections of man and domesticated animals. During this time it was shown that at least a partial immunity to reinfection was

acquired through recovery from various parasitic diseases. The study of immunity in parasitic infections took its first form and direction with the publication of Taliaferro's book in 1929. In considering these newer observations, Culbertson takes up natural resistance as host-parasite relationships, host restriction among parasites, the factors influencing natural resistance, such as genetic constitution, age, sex and reproduction, intercurrent infection, diet, defensive mechanisms of the host and invasive mechanisms of the parasite. Age resistance is elucidated by examples, and explanations are given. Specifically acquired immunity takes up immunity acquired by infections and "premunition" in immunity, a term proposed by Sergent in 1924 to describe a form of resistance which depends on the mutual tolerance of the host and parasite—the resistant state is contemporaneous with the latent infection and ceases with cure. Further, the immunity acquired by vaccination with killed or avirulent organisms and that acquired passively by injection of the immune system are presented. The requisites for the immune response, parasites which elicit immunity, mechanisms of specific immunity and the methods of demonstrating immunity conclude part one. Immunity in specific diseases occupies the main pages of this volume including the amoebiases, the Leishmaniases, the trypanosomiases, the malarias, the coccidioses, the trematodiases, the cestodiases, the nematodiases and the response to arthropods. Finally, a third chapter of applied immunology takes up the classification of parasites, vaccination against parasites and the diagnosis of parasitic infection. Every student of immunology should read Taliaferro's book and then Culbertson's for a rounded knowledge of this subject since Culbertson's text presupposes a knowledge of Taliaferro's. As a readable text, it is also well presented and will prove a valuable and elucidating companion for those interested in this subject.

The nominal cost makes it attractive and the make-up is pleasing to the reader, although illustrations and tabulations are few, and advisedly so for a text of this type. However, the descriptive matter is clear and attractive. The author and Columbia Press have done well in contributing this treatise for students and professionals interested in acquiring knowledge on a subject usually neglected because not readily accessible in understandable form.

ELEANOR METHENY: *Breathing Capacity and Grip Strength of Preschool Children. Pp. vi + 207, University of Iowa Studies: Studies in Child Welfare, University of Iowa Press, Iowa City, Iowa, 1940, paper.*

By DICKINSON W. RICHARDS, JR.

This monograph, one of a series on child welfare at the University of Iowa, is a statistical study of measurements of "breathing capacity" (that is, vital capac-

ity) and grip strength, as carried out in a group of 169 children between the ages of two and one-half to six and one-half years; and of certain correlations of these measurements, with others such as age, various aspects of body size, intellectual capacity and health.

The author has worked out ingenious modifications of the spirometer and dynamometer, adapted to obtain best results in young children.

Body height yielded the highest correlation with breathing capacity. The performance of boys exceeded that of girls, even when height differences were eliminated. Regression formulae are given, based on age and height. The mean values found are somewhat higher than those reported by other investigators, perhaps because of improvements in technique.

No relationship was found between breathing capacity and intelligence quotients, or between breathing capacity and health of the child.

Height was found to have the highest relationship to grip strength, of any of 13 anthropometric measures so studied. There was no relation to intelligence quotients. The performance of boys exceeded that of girls. The findings suggested that low grip strength might indicate a lowered state of health.

One or two questions might be raised regarding details of the work, such as, for example, why breathing capacity is expressed in cubic inches, whereas in all other measurements the metric system is used.

The only important conclusion concerns the use of "breathing capacity" for the more familiar vital capacity. While the maximum amplitude of a single breath is not a "vital" capacity, neither is it the "breathing" capacity, as it represents only amplitude or lung volume, does not register the dimension of time, and therefore is only partially correlated with the true capacity for "breathing" or pulmonary ventilation. Furthermore, breathing capacity is already in common use to express just this function, that is, maximum ventilation per unit of time. It would seem wiser to hold to the traditional term vital capacity, as better known and just as accurate. Vital capacity is not a perfect name for the function, but it has the authority of venerability, and also that of its distinguished originator, John Hutchinson, and certainly should not be displaced until a better term can be found.

JULIUS FRIEDRICH VON FINCK: *Die Wirbeltuberkulose und ihre Heilung. Pp. 214, with 122 illustrations, 1940, Ferdinand Enke Verlag, Stuttgart, paper, RM 18.*

By MATHER CLEVELAND AND FREDERICK R. THOMPSON

The author reports his theories and methods of treatment based on forty years of experience in treating 1,250 cases of tuberculosis of the spine. The patients lie on their backs on posterior plaster shells and are immobilized from head

to knees. Only the arms are free. Doctor von Finck feels that the basic tuberculous process can be arrested in one and one-half years by this more complete conservative method of immobilization. Arthrodesis of the spine is not mentioned.

Of great interest to orthopedic surgeons in this country is the manner in which the clinical appearance of the gibbus is corrected. Photographs are reproduced to demonstrate this. Roentgenograms demonstrate that this correction takes place in the compensatory curve just above and below the diseased vertebrae and not at the site of the destruction. The author stresses that the diseased area must not be pulled apart to obtain the correction but must be compressed to hasten its healing. One is left with the thought that if a gibbus or kyphos can be so surely corrected it would be well to combine this with a subsequent arthrodesis of the spine.

No statistics are given as to mortality, length of hospitalization or follow-up results. One is left with the feeling that an interesting mechanical concept in the treatment of tuberculosis of the spine has been presented, but to review 1,250 cases of tuberculosis of the spine with no mention as to their eventual fate or of any of the complications encountered during their treatment is, to say the least, quite amazing.

Books Received

LUCIE JESSNER AND V. GERARD RYAN: Shock Treatment in Psychiatry: A Manual. With Introduction by Harry C. Solomon. Pp. xv + 149, New York, Grune & Stratton, 1941, cloth.

LEOPOLD LICHTWITZ: Functional Pathology. Pp. xiv + 567, with 157 figures and 39 tables, New York, Grune & Stratton, 1941, cloth, $8.75.

The March of Medicine. New York Academy of Medicine Lectures to the Laity, 1941. Pp. xiv + 154, New York, Columbia University Press, 1941, cloth, $2.00.

National Research Council Report of Committee on Drug Addiction, 1929–1941, and Collected Reprints, 1930–1941. Pp. xxx + 1581, fabrikoid.

Primera Convención de Tisiología del Consejo Nacional de Tuberculosis de la Republica de Cuba, Enero, 1939. Talleres Tipograficos de Carasa y Cia., Brasil 54–56 (Antes Tte. Rey), La Habana.

AMERICAN TRUDEAU SOCIETY

Eastern Section

The 1941 Fall meeting of the Eastern Section of the American Trudeau Society was held at the Hudson County Tuberculosis Hospital, Jersey City, New Jersey, on October 31 and November 1, 1941.

The total attendance at the meeting was 191. This comprised 88 members of the Eastern Section and 103 guests. It was the largest gathering to attend any of the Eastern Section's Fall meetings.

The Section has 273 members. Of them 197 are active and 76 are associate members.

Business Session: The report of the membership committee, appointed in 1940, was adopted. The substance of the report was that the Eastern Section would have two membership classes: the active class and the associate class. The active class shall comprise those who are members of the parent organization, American Trudeau Society. The associate class shall comprise those who are not members of the parent organization but who have a degree in medicine and a special interest in tuberculosis and diseases of the chest. This latter class shall have all the privileges of the active class except that they shall not hold office. The duration of associate membership shall be limited to a period of three years. The dues for members of the associate class shall be the same as dues for the members of the active class, namely $1.00 per year.

At the 1940 meeting of the Eastern Section two resolutions were forwarded to the parent organization, American Trudeau Society. The one considered the present status of "Compensation in Tuberculosis in the Different States." The other considered "Under What Conditions Is Tuberculosis a Disease Due to Occupation." The American Trudeau Society had referred these resolutions to its Committee on Industrial Tuberculosis, of which Dr. Leopold Brahdy is Chairman. Doctor Brahdy was present and submitted an informal progress report of the activities of his Committee on Industrial Tuberculosis. He stated that a formal report would probably be ready for Philadelphia, Pennsylvania.

The following officers were elected for the year 1942: Dr. William J. Ryan, Rockland County Sanatorium, Pomona, New York, Chairman; Dr. Victor F. Cullen, State Sanatorium, Maryland, Vice-Chairman; Dr. James C. Walsh, Nassau County Sanatorium, Farmingdale, New York, Secretary-Treasurer.

ERRATA

Volume XLV, No. 1, January, 1942

In the article by Philip H. Pierson on "Solitary Foci of Tuberculosis" the legends carried at the bottom of page 86 for illustrations shown on page 87 should read as follows:

FIG. 22 (left upper). Case 8. Circumscribed, discrete nodule in center of right lung.

FIG. 23 (right upper). Case 8. Caseous nodule, outer portion left lung, under third rib.

FIG. 24 (left upper middle). Case 8. Gross specimen, caseous nodule, right lung.

FIG. 25 (right upper middle). Case 8. Low power microphotograph of nontuberculous bronchiectatic pocket, right lung.

FIG. 26 (left lower middle). Case 8. Higher magnification showing the bronchus leading to this.

FIG. 27 (right lower middle). Case 8. Higher magnification showing bronchial epithelium.

FIG. 28 (left lower). Case 8. Gross specimen. Caseous nodule, left lung.

FIG. 29 (right lower). Case 8. Microphotograph showing fibrocaseous nodule, left lung.

NONTUBERCULOUS PULMONARY INFECTIONS COMPLICATING PULMONARY TUBERCULOSIS[1]

OTTO S. BAUM AND J. BURNS AMBERSON, JR.

INTRODUCTION

Within the past three years we have observed with special attention a considerable number of nontuberculous pulmonary infections complicating various types of pulmonary tuberculosis. The effect on the course of the tuberculous disease in some cases was striking; in others, inconsequential. Certain fundamental questions suggested themselves. In such circumstances, what are the most important factors leading to activation of a tuberculous lesion? What type of tuberculous lesion is more likely to be influenced by intercurrent infection? Does chemotherapy of pneumonia influence the effect thereof on the course of the complicating tuberculosis? These and other interesting problems arose during this study.

The literature regarding the effect of intercurrent infection on coexisting tuberculous disease, or on subsequent development thereof, is relatively meagre. To be sure, the relation of lung abscess and gangrene to tuberculosis has been intensively studied by French writers. However, there is little information regarding the effect of banal pneumonia, except for the insistence of some writers that it is slight or absent. There is a similar vagueness regarding bronchiectasis.

We were prompted, therefore, to examine the case records in the files of the Tuberculosis Service of Bellevue Hospital, from 1930 to early 1941. All cases filed under a combined diagnosis of tuberculosis and lobar pneumonia, bronchopneumonia, suppurative pneumonia, lung abscess or bronchiectasis were examined. In order to avoid confusion it was decided to exclude all cases of nontuberculous pulmonary infection associated with or caused by endobronchial tuberculosis, active or healed; also, infections related to bronchial distortion (kinking) and to neoplasms encroaching on the bronchial lumen. The study of the bronchiectasis group excludes all cases of known and suspected posttuberculous bronchiectasis, that is, of bronchial dilatation and distortion caused by preceding parenchymal tuberculosis, such as one often finds in areas of fibroid tuberculosis.

A few cases registered in the Tuberculosis Service before 1930 are included in the survey, having been held in the files for their special interest. Some of the patients hospitalized between 1938 and 1939 and most of those admitted between 1939 and 1941 were observed and followed during their hospital course by the

[1] From the Tuberculosis Service, First Medical Division, Bellevue Hospital, and the Department of Medicine, Columbia University, College of Physicians and Surgeons, New York City.

junior author. (Practically all the patients were seen at one time during their hospital stay by the senior author.)

In reviewing the literature we have dealt for the most part with articles appearing after 1930. Mention is also made of some earlier works, particularly texts. Certain implications on the relation of influenza to tuberculosis and on mixed infection in tuberculosis are briefly considered.

The cases have been divided into three groups: the first including lobar pneumonia and bronchopneumonia, (the latter including nonsuppurative aspiration pneumonia); the second including lung abscess and suppurative pneumonia; and the third, bronchiectasis. Isolated cases will be found in more than one group for reasons which will become obvious. The three groups will be considered separately. Conclusions about each group are summarized at the end of the report.

PNEUMONIA AND TUBERCULOSIS

Considerable confusion exists in the earlier literature between nontuberculous pneumonia and tuberculous pneumonia of gelatinous or caseous nature. The confusion is sometimes further increased by the use of the term epituberculosis, a term of doubtful appropriateness. A number of writers, among them Fränkel (1), v. Bergmann and Stähelin (2), Schröder (3), *et al.*, allude to this, and observe that the evaluation of any effect of croupous pneumonia on tuberculosis must be based on adequate diagnostic criteria. That one of the most important of these, namely, roentgen examination, was not available to the majority of writers prior to 1900 is obvious. Some of the reports, such as those of Finkler (quoted by Schröder (3)) describing the rapid progression of lobar pneumonia to caseous tuberculosis, probably deal with an initial tuberculous pneumonia. On the other hand, a statement such as that of Fishberg (4), that "bronchopneumonia occurring in tuberculous patients is almost invariably of a caseous nature . . . ," must be recognized to have distinct exceptions. It is evident, therefore, that there is a fundamental difficulty in evaluating most of the earlier reports, particularly when, as is usual, series of cases are discussed without giving detailed studies of individual cases.

The incidence of pneumonia in the tuberculous population has been considered to be small. Fränkel saw 15 cases in 3,250 tuberculous individuals (0.46 per cent) and contrasts this with an incidence of 3.5 per cent in 21,430 cases of various internal diseases seen in his clinic. Schröder observed only 2 cases in 6,000 tuberculous patients and Halbron (quoted by Schröder (3)), v. Bergmann and Stähelin, and Hochstetter (5) also give a low incidence. Conversely in large series of pneumonias relatively few cases of complicating tuberculosis are reported. Fränkel observed 15 in 760 cases of pneumonia. Finland (6) reports 29 cases of tuberculosis with positive sputum in a series of 3,682 cases of pneumonia. Moore *et al.* (7) in a recent review report 24 cases of "pulmonary tuberculosis, recurrent pleurisy or pneumoconiosis" in 1,469 patients with pneumonia. Various reasons have been proposed, some of the older reports actually assigning a protective rôle to the tuberculous disease. The most likely

explanations would seem to be the sheltered life of the tuberculous population (Miller), and the provisions for isolation of patients suffering from tuberculosis.

In the consideration of the effect of pneumonia on tuberculosis, there is considerable divergence of opinion. Fränkel, v. Bergmann and Stähelin, Stähelin, Schröder, Miller (8), v. Czyhlarz (quoted by Schröder(3)), Hochstetter, Fishberg, Orr (9) and others believe that the course of the pneumonia is unchanged and that it usually exerts no influence on the tuberculosis. Finkler is quoted as calling attention to the possibility of subsequent caseous pneumonia and haematogenous generalization as a direct result of the pneumonia. Courmont and Boissel are quoted by Weissfeiler (10) as stating that pneumococcal infection aggravates the course of tuberculosis. Flick (11) mentions that one-fifth of the cases of tuberculosis gave a preceding history of pneumonia. Tendeloo (12), however, notes that Jurgensen's 60 of 5,738, the Stockholm 36 of 2,616, the Basle 4 of 230 cases of pneumonia which resulted in tuberculosis all must be evaluated in relation to the possibility that the pneumonia initially was tuberculous. This could be applied to Flick's statement as well. A number of authors, among them Pettit (quoted by Schröder (3)), and later McPhedran (13), believe that pneumonia actually exerts a beneficial influence on tuberculosis.

Lauche (14), Baum (15) and others believe that in certain instances the local damage due to tuberculosis may predispose to localization of pneumonia.

It should be mentioned here that most of these authors place the bronchopneumonias following measles, pertussis, and influenza in a group apart, and feel that they not infrequently lead to activation of tuberculosis. Many believe that the relationship is indirect and based on temporary anergy, decrease in general resistance or exogenous superinfection. However, Weigert (16), in 1886, insisted that flaring-up and generalization of a tuberculous process following measles are not caused by the first two factors mentioned above, but by a nonspecific inflammatory process in the lungs, which may involve the capsule of a caseous lymph node, invade the latter, and thus liberate the tubercle bacilli.

We wish at this point to discuss certain aspects of the causes of activation of a tuberculous focus. (The discussion of this subject is applicable as well to the section on pulmonary suppuration which follows.)

Krause (17) described the fixed tissue capsule of the tubercle as a barrier between the imbedded bacilli and the body. As long as this barrier remains competent, there is complete isolation and no clinical tuberculosis develops. One factor breaking the barrier is local congestion of the surrounding tissues, permitting the establishment of a circulatory "give-and-take." This results in diffusion of toxins from the focus, the adjacent tissues become seeded with tubercle bacilli and active tuberculosis may begin. Tendeloo voices a similar opinion when he states that hyperaemia may activate an old latent tuberculosis. This, he notes, was seen in the hyperaemia caused by war gases, though hyperaemia in this instance may be merely an initial step, complicated by other factors, such as secondary bronchopneumonia or suppuration. Chemical and infectious bronchitis and bronchiolitis may activate a focus either by this means or by

direct inflammation of the focus, which may occur when nontuberculous bronchiolitis abuts against tuberculous broncho-alveolitis.

Pagel (18, 19) and Long (20) attach the greatest significance to the factors causing softening of a caseous tubercle. The latter mentions three factors. The first is the proteolytic action of leucocytes present as a response to tubercle bacilli or to secondary bacterial invaders. The latter is "not equivalent to suppuration" and is not believed to occur frequently. A second factor is that of heightened allergy, which is discounted by Long because many cases are relatively anergic in their terminal phases when maximum softening occurs. The third factor concerns multiplication of tubercle bacilli prior to actual softening. Any stimulus causing such multiplication may result in softening. (Hyperaemia might constitute such a stimulus.)

Pagel (19) concluded on experimental grounds that liquefaction is an allergic phenomenon, dependent on the presence of tubercle bacilli and following their rapid multiplication. The part played in this process by "hetero-allergy," that is, by the heightened response of the tuberculin sensitive individual to bacterial antigens other than produced by the tubercle bacillus, was not clear, at least as applied to man.

In relation to this, the experimental work of Weissfeiler *et al.* (10, 21, 22) is of interest. In infecting tuberculous rabbits with pneumococci or staphylococci, he found that the reaction of the animal to the cocci had a more exudative character, took a slower course and tended more to necrosis than the reaction of healthy animals. He ascribed this to hetero-allergy due to the tuberculous infection. It should be noted that the inoculations were made subcutaneously or intraperitoneally. When Bieling and Oelrichs (23) infected tuberculous rabbits by the intratracheal route, the reaction was more violent than in healthy animals, but the infiltration thus formed vanished more quickly in the tuberculous animals. They demonstrated no necroses. Whether these experimental data are applicable to man is again doubtful.

In the light of the theoretical aspects of the causes of activation of tuberculosis, Pagel's (18) case report of a tuberculous patient dying of pneumococcal pneumonia is of great interest. At postmortem examination an encapsulated caseous focus in the centre of a lobe showing gray hepatization was seen to be partly liquefied, and drained by a small bronchus containing purulent exudate. Microscopical examination showed purulent exudate with leucocytes and many pneumococci covering the wall of the cavity and invading the caseous focus, which showed small numbers of tubercle bacilli. In this case, therefore, the observations suggest that liquefaction was due to disruption of the capsule, possibly by the pneumococci, and to proteolytic action of leucocytes, and not to multiplication of tubercle bacilli. It is unfortunate, as will be seen from later discussion, that there was no typing of the pneumococci in this case.

A factor which is not discussed to any great extent by these writers is nontuberculous pulmonary suppuration. As will be shown later, suppurative disease has been found repeatedly to be responsible for activation of a tuberculous process, the mechanism most likely being destruction of the capsule with subse-

quent liberation of tubercle bacilli. The part played by this type of tissue reaction in pneumonia will be elucidated below.

A number of authors have written extensively about the subject of necrosis of lung tissue following pneumonia. Ischaemic necrosis is described in case reports of Kessel (24) and Reinisch (25) and in Rosenthal's summary of the case reports up to 1907 (quoted by Kessel *et al.* (14, 24, 25, 28)). The pathogenesis of such a lesion is explained by these authors as dependent on several factors acting together. Slowing of the circulation, increased viscosity of the blood, compression of capillaries by alveolar exudate and subsequent capillary thrombosis, thrombosis of major branches of the pulmonary artery on the basis of a preceding arteritis all may contribute, resulting in aputrid anaemic necrosis. The subsequent course of such lesions depends as a rule on superinfection by secondary organisms. A toxic bacterial factor is thought by Letulle (26) to be another causative factor in the production of ischaemic necrosis, expressed in injury to vessel walls without actual infection thereof.

Letulle and Bezançon describe dissecting necrotic pneumonia (*pneumonie dissequante necrotique*) as a pathological entity. This occurs rarely in cases of pneumonia, on the basis of coagulative necrosis, followed by dissection, then by liquefaction or sequestration. These authors noted that the various stages may exist side by side, without a definite anatomical pattern such as is usually seen in ischaemic necrosis. It is noteworthy that one of their cases had coexisting tuberculosis and diabetes mellitus, as did the case described by Moolten (28). A mixed bacterial flora was thought to be an important aetiological factor. Moolten's case is of great interest to us, in that he describes destruction of the capsule of an old tuberculous focus with resulting bronchogenic tuberculous spread.

Another important approach to this subject lies in the identification of the tissue reaction according to the specific bacterial agent. Interstitial invasion and reaction seem to be properties which are frequently associated with the tendency to suppuration. It is well known that interstitial invasion is particularly prominent in infections of the lung with haemolytic streptococci, seen most frequently in childhood. Other interstitial invaders are the Friedlander bacillus, anaerobic mouth organisms, and less frequently the staphylococcus. These are occasional secondary invaders of preëxisting bronchitides and pneumonias. Pneumococci, on the other hand, are primarily alveolar organisms (Avery, Cole, (quoted by Tendeloo (12)), Tendeloo), and interstitial invasion by these organisms is relatively infrequent. An exception to this may be the type-3 pneumococcus, and less so its related type 8. Finland and Sutliffe (29), in studying infections with pneumococcus types 3 and 8, found at postmortem examination necrotic foci in the consolidated areas in one-third of the cases of pneumococcus type-3 lobar pneumonia. They also observed a higher incidence of secondary organisms in the type-3 cases. In a later study Finland (6) reported 3,682 cases of pneumonia caused by all types of pneumococci, noting 96 cases of clinically detected focal purulent complications, with the highest incidence (28 cases) in pneumonias caused by type-3 pneumococci. Finland, Brown and Ruegsegger (30), analyzing

the postmortem findings in 764 cases of pneumococcal pneumonia, found 113 cases of gross or microscopical focal suppuration, most frequent in type 3; 36 cases of ischaemic necrosis, most frequent in type 3; and 75 cases of organization, again most frequent in type 3. Thus it is seen that interstitial invasion, usually a prerequisite to suppuration and organization, is found occasionally in pneumococcal pneumonia and is conspicuous in infections caused by pneumococcus type 3.

Bracken (31) studied the bacteriology of 842 cases of pneumonia occurring between 1935 and 1940 and observed that in recent years more "atypical pneumonias" have been seen. He noted marked increase in the incidence of delayed resolution and ultimate tissue breakdown with formation of multiple abscesses and ascribed this to "mixed infection." He notes a parallel in the pathology of these pneumonias and of post-influenzal bronchopneumonia, with findings of haemorrhagic and purulent pneumonia, interstitial pneumonia, infected vascular thromboses and abscess formation. In this regard it may be pertinent to refer to the observations on tuberculous patients made during the pandemic of influenza in 1918 to 1923. The majority of authors, including Amberson and Peters (32), Hawes (33), Berghoff (34), Sloan (35), Miller (8), Hendricks (36) and Bihler (37), agrees that many cases of activation of quiescent pulmonary tuberculosis and progression of active disease were seen following influenza, particularly post-influenzal bronchopneumonia. Only few, among them Fishberg (38), insist that there was no relationship. Since the underlying pathological processes in post-influenzal bronchopneumonia consist of suppuration and interstitial invasion, usually caused by secondary invaders such as *Streptococcus haemolyticus* and *Haemophilus influenzae*, the basis of activation seems evident. A further possibility exists, namely, that the catarrhal exudation resulting from bronchitis and bronchiolitis washes out tubercle bacilli from quiescent foci communicating with the bronchial tree (Amberson, Baum (15) *et al.*).

There have been two recent reports of pneumococcal pneumonia complicating tuberculosis treated by sulfapyridine. Crawford (39) reports one case and Pedigo and Coleman (40) two, all successfully treated, none showing activation. The latter mention that lack of complete resolution was present in both of their cases, but do not consider this as a possible spread of the tuberculous lesion into the pneumonic lobe. They report an additional case seen at autopsy, with previously unsuspected tuberculosis, showing pneumococcus type 3 in the sputum and blood. No mention is made of the histological character of the tuberculous lesion. They conclude that terminal pneumococcal pneumonia is not infrequent in patients dying of tuberculosis. Our own experience coincides with this.

Finally we may refer to the reports of Leitner (41) on hyperergic eosinophilic infiltrates, a rather vague syndrome, the explanation of which is not generally agreed upon, and of Sampson (42) on rapidly clearing pulmonary consolidation. Both noted pneumonic infiltrations occurring in tuberculous patients, clearing rapidly without significant residue. These were considered to be due to an allergic factor, in the nature of a "tuberculin pneumonia." The striking differences from true nontuberculous pneumonia consisted in the lack of leuco-

cytosis, absence of typable pneumococci or other organisms and, in Leitner's series, a heightened tuberculin reaction as well as an abortive benign course associated with eosinophilia. These reports are of importance in showing the necessity for adopting multiple rigid criteria in the diagnosis of nontuberculous pneumonia complicating tuberculosis.

Analysis of Data

Our series comprises 102 cases of pneumonia developing in 97 patients treated on the wards of the Tuberculosis Service between 1932 and 1941. The majority was seen between 1938 and 1941. Charts and roentgenograms of all patients discharged with the combined diagnosis of pneumonia and tuberculosis were examined and subjected to rigid criteria before inclusion in the series. All cases of tuberculous pneumonia were excluded. All cases of pneumonia related to tuberculous endobronchitis, old or healed, or raising the suspicion of such a background were dropped. Cases about which marked differences of opinion regarding diagnosis are recorded in the chart are likewise not included. Considerable stress was laid on clinical history, laboratory findings and clinical course. In the history great stress was placed on the presence of rigor, rusty sputum and herpes labialis, all of which are rare in uncomplicated tuberculous pneumonia. Laboratory findings, such as the presence of a typable pneumococcus in sputum and blood, and the level of the leucocyte count and polymorphonuclear neutrophile percentage, were weighed in relation to the clinical course. Resolution of pneumonic densities shown in the roentgenogram within a period of time (maximum of three weeks) too rapid to be characteristic of tuberculosis was also evaluated in relation to the clinical course. In a number of cases the clinical diagnosis could be confirmed by postmortem examination.

The diagnosis of tuberculosis was based on clinical, bacteriological and roentgenographic findings.

In grouping all of our cases under the heading of pneumonia, rather than subdividing them into lobar and bronchopneumonia, we have followed the recent clinical analyses of large groups, in which the bacteriological findings and clinical course are stressed, rather than the roentgenographic and pathological findings. This is justified, in our opinion, if only by the abortive effect of early specific therapy noted repeatedly in recent years.

The range of age in this group was from 22 to 72 years, most of the patients being in the upper middle age group. Most of the patients were males. The most frequent complicating diseases were chronic alcoholism with its attendant delirium and pulmonary fibrosis and emphysema.

Lack of space prevents tabulation of individual cases. Instead we have resorted to group-analysis and have appended a number of case summaries illustrative of the various categories. We have grouped the cases in four categories of degree of activation: definite, probable, doubtful and none. Judgment of assigning the cases to the various categories has been necessarily rather subjective, but we tried to set up definite though arbitrary criteria for such placement.

Definite activation was thought to have taken place when (*1*) there was post-

mortem evidence of recent activation or (*2*) when, following pneumonia, pulmonary tuberculosis, which previously had been stationary or latent, became progressive.

To the category of probable activation were assigned cases in which (*1*) previously inactive pulmonary tuberculosis showed signs of activity, though not of progression; (*2*) there was spread of previously active tuberculosis coinciding with the pneumonia; and (*3*) early death was due apparently to progressive tuberculosis, although postmortem examination was lacking.

The category of doubtful activation included (*1*) cases of tuberculosis showing temporarily a positive sputum during the course of pneumonia, (*2*) cases showing residual areas of density in the roentgenogram, in which differentiation between spread of tuberculosis and postpneumonic pulmonary fibrosis was not possible, and (*3*) cases showing progression of tuberculosis later than one month but sooner than one year after subsidence of the pneumonia.

No activation was considered to have taken place (*1*) when there was no

TABLE 1

Pneumonia associated with tuberculosis

Definite activation of tuberculosis	8
Due to pneumonia	4
Due to suppuration following pneumonia	4
Probable activation of tuberculosis	10
Due to pneumonia	9
Due to suppuration following pneumonia	1
Doubtful activation of tuberculosis	11
No activation of tuberculosis	65
Not known	8

change in the tuberculous lesion or its activity, or (*2*) when progression of the tuberculosis occurred later than one year after subsidence of pneumonia, the latter having left behind no suppurative lung disease.

The degree of activation was considered to be unknown when death occurred too soon to show an effect clinically and when no postmortem examination was done. It was also considered unknown when no adequate information was at hand regarding the status of tuberculosis at the time the pneumonia took place, even though there was progressive tuberculosis following the pneumonia (3 cases).

Table 1 shows the number of cases in each category. It will be seen that in 4 of 8 cases considered to show definite activation, suppuration occurred in an initially non-suppurative pneumonia, and that activation was thought to be due to the suppurative element. Such a suppurative factor was present in one of 10 cases of probable activation. None of the doubtful cases showed suppuration. However, there was a striking incidence of slow resolution with residues of an unknown nature in this group, and practically all these cases had marked fibrosis and emphysema. That this underlying pathological process may retard resolution and favor organization is well known, among the reasons being improper

drainage and impaired blood supply of the affected lung. It is also observed that the roentgen pattern of pneumonia involving a fibrotic and emphysematous lung closely resembles that of tuberculosis. The attendant difficulty of differentiating a spread of tuberculosis from postpneumonic fibrous residues accounts for the relatively large number of cases in this category.

Table 2 shows the predominating organisms in typing and culture of the

TABLE 2

Types of pneumonia association with tuberculosis

TYPE OF ORGANISM	NUMBER OF CASES	DEFINITE ACTIVATION OF TUBERCULOSIS	PROBABLE ACTIVATION OF TUBERCULOSIS	BACTERAEMIA	DEATH
Pneumococci					
1	7	—	2	—	2
2	9	2	1	4	3
3	11	3	1	—	1
5	4	—	1	1	—
6	1	1	—	1	1
7	6	—	—	—	—
8	3	—	—	—	1
14	1	—	—	—	1
17	1	—	1	—	—
18	1	—	1	1	—
19	1	—	—	—	1
21	1	—	—	—	—
23	1	—	—	—	—
25	1	—	—	—	—
Mixed	7	—	2	—	—
Unclassified	7	—	1	1	2
Streptococcus haemolyticus	4	2	—	1	1
Mixed other than pneumococci	7	—	—	—	—
Unknown	29	—	—	—	4
Total	102	8	10	9	17

Total number of blood cultures taken	46
Percentage of patients showing bacteraemia	19.5
Deaths	
Patients receiving specific therapy	9
Patients receiving no specific therapy	8
Total mortality	16.7%

sputum tabulated in relation to activation. It appears that the distribution of types is quite similar to large series of pneumonia reported in the literature. Types 3, 2 and 1 pneumococci predominate, with mixed types (that is, multiple pneumococcic strains none of which was predominant) as frequent as type 1. The group of unclassified pneumococci is largely composed of cases seen before typing sera for all types were available and may include any of the types other than 1 to 8 and 14. Nine cases of bacteraemia were encountered in 46 cases in

which the blood was cultured, an incidence of 19.5 per cent, which again is similar to larger series. The immediate mortality due to pneumonia was 16.7 per cent.

The figures for each type are too small for any significant group-analysis of activation. However, it seems of importance to note the frequency of activation seen in pneumonias due to *Streptococcus haemolyticus*, and to pneumococcus types 3 and 2. The incidence of bacteraemia in the type-2 cases is striking and, since 2 of the 4 bacteraemic cases showed activation, may be of significance. A third case of type-2 pneumonia showed suppuration, which was thought to be responsible for the activation of tuberculosis. The degree of activation exhibited by the cases of *Streptococcus haemolyticus* and pneumococcus type-3 pneumonia is in keeping with the above mentioned data of Finland and the known interstitial invasive power of *Streptococcus haemolyticus*.

An attempt to correlate activation with the presence of secondary invaders was unsuccessful because of insufficient data obtained from sputum cultures.

TABLE 3

Topographic relations of pneumonia and tuberculosis

	DEFINITE AND PROBABLE ACTIVATION OF TUBERCULOSIS	DOUBTFUL AND NO ACTIVATION OF TUBERCULOSIS	REACTION OF TUBERCULOSIS UNKNOWN
Pneumonia in lobe involved by tuberculosis	13	27	
Pneumonia not in lobe involved by tuberculosis	4	49	
Unknown whether pneumonia in tuberculous lobe	1	0	
Total—102	18	76	8

This mechanism is definitely under suspicion as one of the factors contributing to suppuration and consequent activation.

Table 3 shows an attempt to correlate activation with location of the pneumonia relative to the lobe involved by tuberculosis. It is probably significant that in the groups of definite and probable activation, 13 of 18 cases had their pneumonia in the lobe involved by tuberculosis, whereas the ratio was reversed in the groups of doubtful and no activation, 49 of 76 cases showing pneumonia in a lobe clinically and roentgenologically uninvolved by tuberculosis. In addition, a number of the 27 unactivated cases, whose pneumonia was in the lobe involved by tuberculosis, showed the pneumonia in a segment of the lobe uninvolved by tuberculosis. There were, however, several cases with pneumonia in the immediate vicinity of tuberculous disease, which showed no activation.

In table 4 we have tried to evaluate the effect of specific therapy of pneumonia on the degree of activation. Thirteen of 18 cases showing activation received some type of specific therapy, while 29 of 76 cases without activation were treated by chemical, serum or combined therapy. It is doubtful whether any

conclusions can be drawn from these figures. A possibility exists that specific therapy kept alive gravely sick individuals, who would have died without such treatment. Subsequent activation may have been due either to areas of necrosis in the pneumonic lobe or to a markedly lowered resistance.

Table 5 shows the relation of degree of activation to the type of tuberculous disease present initially. Again the figures for certain categories are small and only trends are suggested. It is noteworthy that 5 of 15 cases of predominantly exudative disease showed activation, while only 8 of 47 cases of predominantly

TABLE 4

Treatment of pneumonia in the tuberculous

TREATMENT	DEFINITE AND PROBABLE ACTIVATION OF TUBERCULOSIS	DOUBTFUL AND NO ACTIVATION OF TUBERCULOSIS	REACTION OF TUBERCULOSIS UNKNOWN
Chemotherapy	9	24	
Serum therapy	1	4	
Chemotherapy and serum therapy	3	1	
No specific therapy	5	47	
Total—102	18	76	8

TABLE 5

Pneumonia in different pathological types of tuberculosis

TYPE OF TISSUE DISEASE	ACTIVATION OF TUBERCULOSIS					
	Definite	Probable	Doubtful	None	Unknown	Total
Predominantly exudative	2	3	1	3	3	12
Predominantly productive and fibrotic	5	3	7	31	1	47
Fibrocavernous	0	4	3	7	4	18
Fibrocalcific	0	0	0	17	0	17
Under collapse therapy	0	0	0	6	0	6
Unknown	1	0	0	1	0	2
Total	8	10	11	65	8	102

productive disease were activated. Four of 18 cases of fibrocavernous disease showed activation, relatively a high incidence. Of greatest significance are the groups of fibrocalcific tuberculosis and tuberculosis under collapse therapy. No activation occurred in 17 of the former and 6 of the latter group, even though the pneumonia frequently was in the area of tuberculous disease.

Charts 1 and 2 show the frequency distribution of initial and maximal leucocyte counts and polymorphonuclear neutrophile percentages. The latter appears to be significant in that the curve is definitely skew in the direction of percentages above 84. The range of the leucocyte counts shows that two-thirds of the cases had counts greater than 14,000, but that only two-fifths had maximal

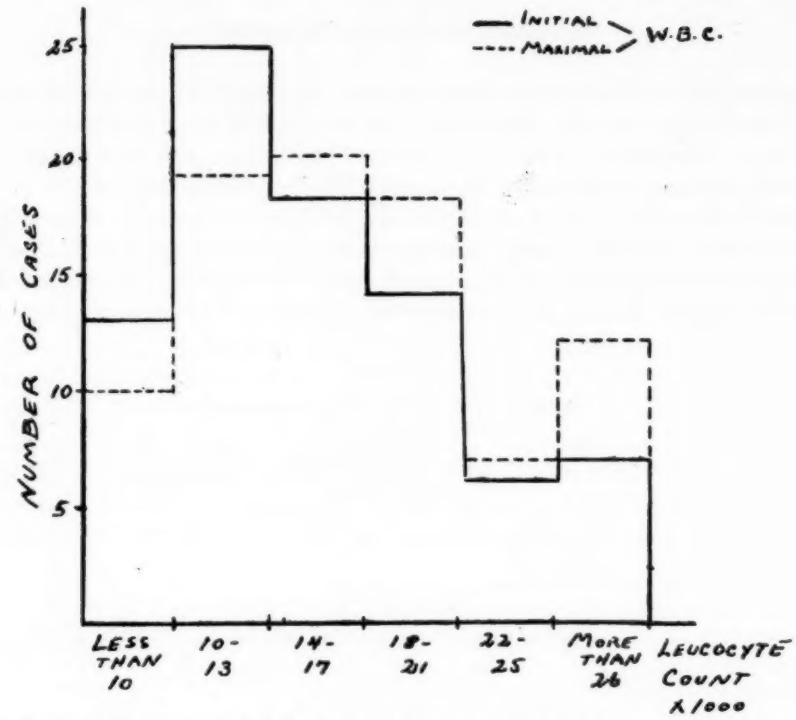

CHART 1. Frequency distribution. Initial and maximal leucocyte counts

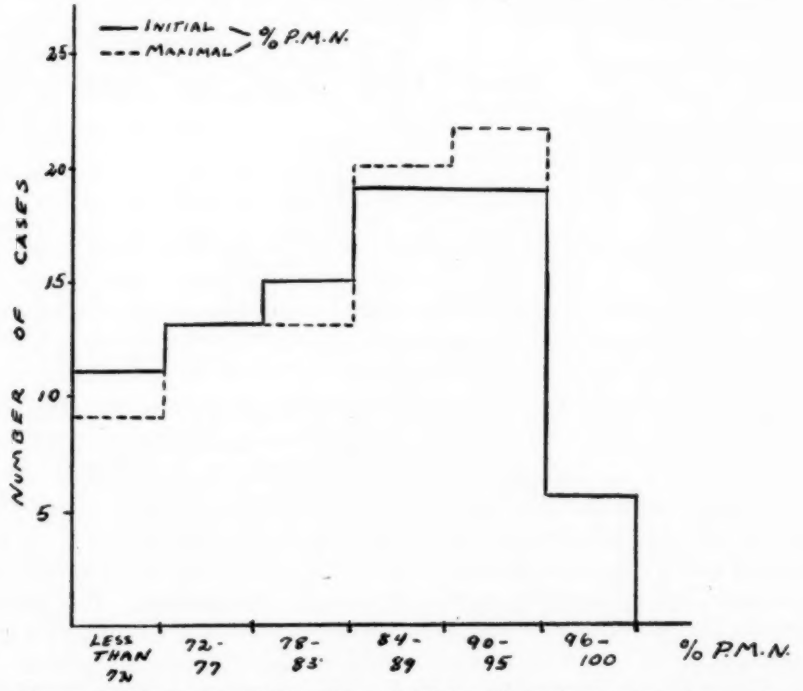

CHART 2. Frequency distribution. Initial and maximal percentages of polymorphonuclear neutrophils

counts over 18,000. The latter is usually considered as the maximal level of the leucocyte count in tuberculous pneumonia, though Medlar (43) has given the range of the leucocyte count in uncomplicated tuberculosis as from 2,500 to 50,750. Nevertheless, the distribution as found in this series parallels that in larger series of pneumonias and expresses the reaction to the nonspecific rather than the tuberculous infection, particularly since only 15 of the cases showed initially a predominantly exudative tuberculous lesion.

Of the outstanding initial symptoms of pneumonia, pleural pain was most frequent, occurring in 69 cases. A true chill was present in 49 cases, rusty sputum in 18, herpes labialis in 14 and frankly bloody sputum in 4. Five cases showed toxic delirium which is practically never seen in tuberculous pneumonia.

In order to clarify our criteria of activation as well as to demonstrate the type of reaction of the tuberculous process to the pneumonia we have selected a representative number of cases from each category for individual presentation.

Cases showing definite and probable activation:

1. *J. M.:* Male, *aet.* forty-five, admitted 1940. No previous respiratory history. One week before admission he developed pain in the left ear. Onset three days before entry with cough, chills, dark sputum, left pleural pain. On physical examination he had acute left catarrhal otitis media, herpes labialis, signs of consolidation over the left upper lobe, dulness at the right apex and moist râles at the right base. Roentgenogram on admission showed a fibrotic tuberculosis in the right apex and dense opacity of consolidation of the left upper lobe. Leucocyte count varied from 8,600 to 26,000, polymorphonuclear neutrophils from 64 to 88 per cent. Sputum typing showed pneumococcus type-2 which was also found on blood culture. A later sputum culture showed *Staphylococcus albus*, *Streptococcus alpha* and diphtheroid bacilli. Sputum was negative for tubercle bacilli on smear and concentration and remained so for two months, though culture of the sputum one month after entry showed tubercle bacilli. He received 18 g. of sulfapyridine by mouth; his temperature dropped by lysis to normal on the fourth day, rising after four days gradually to 102°F. Blood culture was negative. A second course of sulfapyridine had no effect. Two weeks after entry roentgen-ray examination showed a large cavity in the left upper lobe and the sputum gradually became foul; multiple cavities developed which later became confluent. At this time culture of the sputum was positive for tubercle bacilli. On postural drainage sputum became gradually less foul, but two months after entry, it was positive on concentration for tubercle bacilli.

Comment: Case of type-2 pneumococcal pneumonia with bacteraemia, subsequent suppuration and definite activation of tuberculous focus, the abscess cavity being gradually transformed into a tuberculous cavity.

2. *A. G.:* Male, *aet.* fifty-five, admitted 1939–1940. He had known tuberculosis since 1931, with a contracted right upper lobe containing a 3 cm. cavity (figure 1), which gradually closed on sanatorium treatment (figure 2), converting the sputum from positive to negative. He had negative sputum since 1937, when cavity was no longer demonstrable by X-ray. Two weeks before admission he had a chill, followed by fever, rusty sputum, malaise, slight dyspnoea. On physical examination he was acutely ill, febrile and had herpes labialis. Signs of consolidation were present over right upper and lower lobe. A roentgenogram showed increase in size of previously contracted upper lobe with central

rarefaction and a homogeneous density over lower lung field (figure 3). The leucocyte count dropped from 21,000 (polymorphonuclear neutrophils 92 per cent) to 9,800 (polynuclears 88 per cent) with a secondary rise to 19,800 (polynuclears 86 per cent) and an ultimate drop to 8,900 (polynuclears 66 per cent). Sputum typing revealed pneumococcus type-3. Blood culture was negative. Sputum examination for tubercle bacilli yielded 26 negative concentrates in six weeks following pneumonia; thereafter it was repeatedly positive. He received 21 g. of sulfapyridine by mouth in seven days; his temperature dropped to lower level, but remained between 99° and 101°F. for four weeks. Subsequent roentgenograms showed complete clearing of right lower lobe, but progressive enlargement of right upper lobe cavity (figure 4).

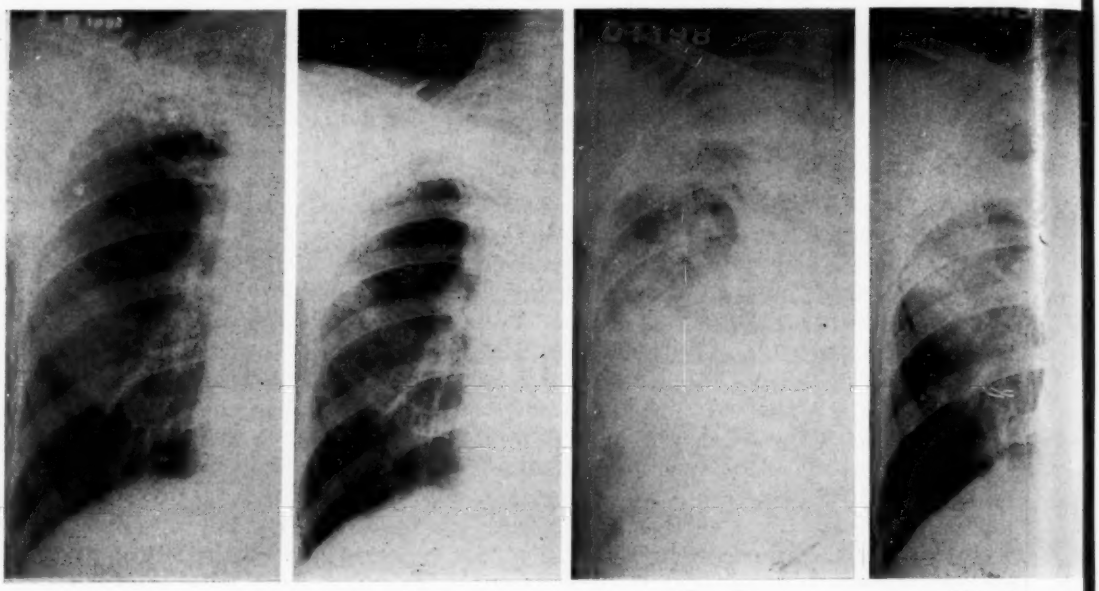

FIG. 1 FIG. 2 FIG. 3 FIG. 4

FIG. 1. Case 2. August 15, 1932. Cavity in periphery of right first anterior interspace.
FIG. 2. Case 2. September 20, 1938. Cavity closed.
FIG. 3. Case 2. November 25, 1939. Admission film after onset of pneumonia.
FIG. 4. Case 2. February 26, 1940. Cavity reopened and larger than at any time previously.

Comment: Case of pneumococcus type-3 pneumonia with reopening of previously closed tuberculous cavity and definite reactivation of tuberculosis.

3. *A. R.:* Male, *aet.* forty, admitted 1940. Onset eight days before admission with upper respiratory infection. On day before admission he developed a shaking chill and right upper chest pain, malaise, cough productive of bloody mucoid sputum. On admission he was acutely ill. There were signs of consolidation with crackling râles over the right upper lobe. A roentgenogram showed dense consolidation of right upper lobe; fine nodular dissemination in lower two-thirds of left lung field. The leucocyte count ranged between 11,600 and 22,400 with 76 to 80 per cent polymorphonuclear neutrophils. On sputum typing, pneumococcus type-18 was found; also in first blood cul-

ture. Sputum was positive for tubercle bacilli. He was given sulfapyridine by mouth and 200,000 units of type-18 rabbit serum intravenously. Temperature dropped by crisis to 100°F., with marked symptomatic improvement and sterilization of blood stream. However, temperature remained between 100° and 101°F., and roentgenograms showed clearing of right upper lobe leaving residual cavity with adjacent exudative areas, nodular spread to right lower lung field and slight increase in nodular spread in left lung. At discharge to a sanatorium three weeks later no change had occurred in these lesions.

Comment: Case of pneumococcus type-18 pneumonia with bacteraemia and probable activation of underlying exudative tuberculosis.

Case showing doubtful activation:

4. *G. M.:* Male, *aet.* thirty-two, admitted 1932 and 1933. Known tuberculosis since 1931, sputa negative since early in 1932. Two days before entry he had sudden onset of cough, blood-streaked sputum, weakness and sweats. On physical examination he was acutely ill, irrational and had a temperature of 104.6°F. There were signs of consolidation over right lower lobe with pleural friction rub and few râles at right apex and left base. A roentgenogram showed diffuse homogeneous shadow of consolidation over lower two-thirds of right lung and a fibrocavernous lesion above the second rib on the right. His leucocyte count dropped from 13,900 with 96 per cent polymorphonuclear neutrophils, to 11,000 with 67 per cent polynuclears. Sputum typing was not done and no blood culture was obtained. Sputum was positive for tubercle bacilli. His temperature remained around 104°F. until seven days after admission when it suddenly dropped by crisis, with marked clinical improvement, and normal temperature thereafter. Roentgenograms showed complete clearing of pneumonia, leaving residual fibrocavernous disease as before. Sputum remained positive. There was no significant change in lesion on subsequent admissions when sputa were repeatedly positive.

Comment: Case of fibrocavernous tuberculosis of right upper lobe and pneumonia of right lower lobe. Sputum negative six months previously was positive on entry and following pneumonia. No change in lesion. Doubtful activation.

Case showing no activation:

5. *J. M.:* Male, *aet.* fifty-five, admitted 1940. Onset of tuberculosis was in 1928, diagnosed 1932, treated with right artificial pneumothorax since 1935 (figure 5). Sputum became negative after pneumothorax was begun. Last pneumothorax refill was given thirteen days before admission (figure 6). On day before entry he had sudden shaking chill, followed by pain in right anterior chest close to sternum, cough and rusty sputum. He was acutely ill, dyspnoeic and cyanotic. His temperature was 104.4°F. He had herpes labialis. There were signs of pneumothorax on right, except in second anterior interspace where diminished breath sounds and few medium moist râles were heard. A roentgenogram showed selective, 50 per cent collapse of right upper lobe by pneumothorax with some string adhesions. In area of previous tuberculous disease at the base of the upper lobe there was slight haziness, which two days later developed into definite patchy consolidation (figure 7). The left lung showed scattered calcified foci in the upper third. Leucocyte count of 22,400 with 86 per cent polymorphonuclear neutrophils dropped in two days to 7,600 with 68 per cent polynuclears, and remained normal thereafter. Sputum typing revealed pneumococcus types 19 and 24 on repeated examinations before and after treatment. Sputum was negative for tubercle bacilli

on concentration during hospital stay and has remained so in clinic. On day following entry sulfapyridine was given by mouth, a total of 18 g. in four days. Temperature dropped by lysis to normal in forty-eight hours and remained normal. Roentgenograms showed progressive clearing of the pneumonic area, complete in one week after admission (figure 8).

Comment: Case of pneumococcus types 19 and 24 pneumonia in collapsed lobe in area of previous tuberculous disease. No activation of tuberculosis.

FIG. 5

FIG. 6

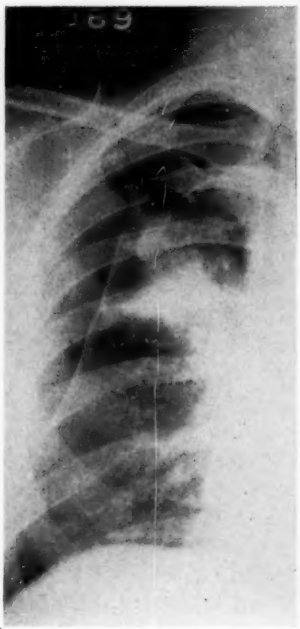

FIG. 7

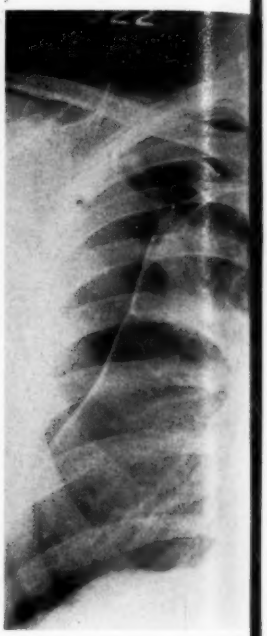

FIG. 8

FIG. 5. Case 5. July 29, 1935. Before pneumothorax.
FIG. 6. Case 5. January 9, 1940. Before onset of pneumonia.
FIG. 7. Case 5. February 8, 1940. Maximal extent of pneumonia.
FIG. 8. Case 5. February 26, 1940. After clearing of pneumonia.

Discussion

Certain definite conclusions may be drawn from our data and others are suggested. Pneumonia is not rare in the tuberculous population. Numerous reports to the contrary are probably to be explained by the fact that many such studies have been based on experience in sanatoria, where the sheltered life and other conditions guard against pneumonia. When pneumonia occurs, it is not always innocuous to the tuberculous lesion. While it is true that the great majority of tuberculous lesions is not activated by a complicating pneumonia, certain definite mechanisms exist whereby tuberculosis may become activated. The first, and probably the most important, is tissue necrosis, whether as a result of ischaemia, toxic cellular damage or suppuration due to the nature of

the organism primarily responsible or entering as a secondary invader. If such necrosis invades an encapsulated tuberculous focus, the result is liberation of imprisoned bacilli and activation of the disease. A second mechanism, also of considerable importance, is the catarrhal exudation from the bronchial or bronchiolar wall during the course of the pneumonia. This may wash out bacilli from a cavity wall, or from an area of nonencapsulated tuberculous broncho-alveolitis, and result in spread of previously quiescent disease. A third concept, which is not clinically demonstrable, though sound in reason by analogy, is that hyperaemia surrounding a tuberculous focus, particularly if the latter is not perfectly encapsulated, may result in multiplication of contained tubercle bacilli with resulting softening, liquefaction and excavation. "Hetero-allergy" as a possible mechanism of activation is more markedly in the realm of speculation. Finally the effect of decrease in general resistance should be mentioned, though this too is elusive and not susceptible of proof.

We believe that the reason for the failure of pneumonia to activate the majority of tuberculous cases lies in the site of attack by the most frequent infecting organism, the pneumococcus. This organism is primarily an alveolar pathogen and interstitial invasion is the exception rather than the rule, conspicuous only in type 3. Whether bacteraemia actually is an index of invasiveness is not certain though possible. It is suggestive that most of the bacteraemic cases in our series showed some degree of activation.

LUNG ABSCESS AND TUBERCULOSIS

The subject of pulmonary suppuration in its relation to tuberculosis has been more extensively studied than any other type of pneumonia. Particularly the French writers have contributed to an understanding of the forms of the relationship. Relatively few cases are reported in the American literature, and the conclusions drawn are largely derivative. (The term "pulmonary suppuration" as used here refers to a disease appearing *de novo*, without preceding nonsuppurative pulmonary infection, and not secondary to a tuberculous bronchial lesion or a bronchial neoplasm.)

In the nineteenth century Bayle (quoted by Murray (44)) and Laennec (45) referred to cases of terminal gangrene involving the walls of tuberculous cavities. Lees (quoted by Murray (44)) in 1842 noted a similar case, and Courveilhier (quoted by Murray (44)) in 1852 stated that gangrene secondary to tuberculous arteritis could occur in noncavitary forms of tuberculosis. Thereafter attention was diverted from this subject by the conjectures of Koch (quoted by Hollo (46)), who suggested that mixed infection complicating tuberculosis may be responsible for cavitary progression of tuberculosis.

This subject thereafter was of paramount interest and many writers reported sputum and blood cultural studies in cases of cavitary tuberculosis. Sata (47), Ophüls (48), Prudden (49), Teissier (quoted by Hektoen (50)), Hektoen (50), Hayes (51), Brauer and Peters (52), Gräff (53), and Sylla and Kairies (54) among others, on the basis of experimental and clinical investigation, insisted that mixed infection plays a definite rôle both in the formation of cavities and in the

systemic toxaemic manifestations during the course of tuberculosis. We will not analyze the evidence propounded by these authors, since that has been done systematically and thoroughly by Hollo (46) who concludes that no methods of investigation have yielded any convincing proof that mixed infection is a part of the usual pathological picture of pulmonary tuberculosis. (We are again not alluding to the mixed infections known to complicate bronchostenosis or posttuberculous bronchiectasis.)

Isolated reports of the coexistence of pulmonary suppuration and tuberculosis are found in the texts of Fränkel (1) and Schröder (3). The former noted 7 tuberculous cases developing terminal gangrene and 4 cases of gangrene, 3 in diabetics, which subsequently developed tuberculosis. Schröder saw only one case of gangrene in 4,716 tuberculous patients, but quotes Echhorst who saw 17 cases of combined disease in 121 cases of gangrene. Single reports of Lebert, v. Sokalowski, and Packard are also quoted by Schröder. Schröder mentions that cases of suppurative and organizing pneumonia in their subacute phase may activate a latent tuberculous lesion, leading usually to fibroid phthisis, the extension of which is limited by the cirrhotic process.

Most of the subsequent reports are found in the French literature. It should be mentioned that in the older literature, as well as the more recent French articles, the term pulmonary gangrene is apparently used synonymously with acute (putrid) lung abscess.

Renand, Roubier, Desplans (quoted by Murray (44)), Caussade *et al.* (55, 56), (Lemiere and Bernard (57), Gräff (53), and Roch and Bickel (quoted by Murray (44)) report individual cases of terminal gangrene associated with preëxisting tuberculosis, as well as a number of cases of combined disease occurring without immediate fatal termination. Courcoux and Lelong (58) believe that the two diseases follow an independent course without influencing each other, but this view is not shared by the majority of subsequent writers.

Albot and Adéle (59) in 1931 reviewed the French literature and from the 30 reported cases gleaned the following three possibilities for simultaneous occurrence of the two diseases. First, gangrene may develop in the walls of a tuberculous cavity. Second, it may develop independently from an existing chronic tuberculosis. Third, the development of gangrene may be associated with exacerbation of tuberculosis and subsequent simultaneous progression of the two diseases.

Sergent and his coworkers (60–65) have written extensively on this subject during the past ten years and, at the time of the last report, had collected 29 cases from their clinic, an incidence of 8 per cent of the abscesses seen. Couve (64) presented Sergent's viewpoints in his thesis, in which he proposed two mechanisms to explain the development of tuberculosis in a case of pulmonary suppuration. The first consists of local action of the suppurative process on a preëxisting tuberculous focus, either by necrosis of the capsule or by nondestructive inflammatory changes in the periphery. The Sergent school believes that the second mechanism is much more frequent, this being a change in host soil and loss of general resistance, resulting in exacerbation of old haematogenous

tuberculous foci, which may be distant from the site of suppurative disease. This thesis is supported by case reports of Sergent (60, 62), Sergent, Courilsky and Couve (61), Sergent, Gaspar and Tsui (63), Pimienta (66) and Durand (67).

The opposing viewpoint, that local destructive action of the suppurative lesion is primarily responsible for activation of tuberculous foci previously present at the site of suppuration, is held by Ameuille (68), Léon-Kindberg (69), Huguenin and Boucabeille (70), Bezançon *et al.* (71), Characopos (72) and others. These writers conclude that tuberculosis usually develops in direct connection with the suppuration, in the neighborhood of the suppurative process. As a rule, at the onset, tuberculosis so developing produces no clinical or distinct radiological signs, manifesting itself only by positive sputum. They believe that Sergent's thesis holds true in rare cases, and only when tuberculosis develops locally or in some other part of the lung after healing of the suppurative lesion.

A further mechanism explaining the development of tuberculosis after suppurative disease has been present for some time was first proposed by Ameuille (quoted by Dubois-Verlière (73)), namely, exogenous superinfection. Antoine, Laval and Lemièrre (quoted by Dubois-Verlière (73)), Bezançon (71), and Dubois-Verlière and Hercelles (73) report such cases. Bernard and Coste (74) also mention this possibility.

Finally Léon-Kindberg and Israel (75) and Dubois-Verlière and Hercelles (73) call attention to the possibility that acid-fast organisms recovered from suppurative lesions which show no radiological evidence of tuberculosis may be nonpathogenic. They urge that in such cases animal inoculation be done in order to determine the virulence of such organisms.

Reports of this nature in the American literature are few, and only isolated cases have been described. Neuhof and Wessler (76) refer to the possibility of coexistence of the two diseases but state that they have not seen any case of lung abscess in which tubercle bacilli were found during the putrid infection.

Murray (44) gives an excellent review of the literature and reports a case of lung abscess followed some time later by bronchogenic and haematogenous tuberculosis. He adds to the mentioned types of relationship the possibility of reactivation of tuberculous mediastinal lymph nodes by secondary infection drained from the abscess area, resulting in haemic dissemination of tubercle bacilli.

Geer (77) reports a case of pulmonary tuberculosis with a supervening gangrene going on to fatal termination. At autopsy wide-spread bronchogenic tuberculosis, tuberculosis of the hilar nodes, and gangrene of the lobe initially showing tuberculosis were found. Oral sepsis was the probable aetiological factor in this case.

Berg and Dieffenbach (78) describe an interesting case in which an abscess involved the tuberculous area of the lung. The latter apparently sloughed completely, since the sputum became negative and surgical drainage did not result in a persistent sinus tract. To insure permanence of the healing they collapsed the affected upper lobe by thoracoplasty.

Analysis of Data

Our series comprises 55 instances of lung abscess and suppurative pneumonia occurring in 54 patients treated on the wards of the Tuberculosis Service between 1926 and 1941. Twenty-five of these cases were observed during the past three years, and only a small number before 1930. Charts and roentgenograms of cases discharged with the combined diagnosis were scrutinized and, as in the pneumonia group, definite criteria for inclusion in the series were followed. Again all cases of abscess and suppuration secondary to active tuberculous endobronchitis or posttuberculous bronchostenosis were excluded from the series. A number of cases with foul sputum and other clinical evidence of suppuration in which tuberculous endobronchial disease was suspected but not proved by bronchoscopy were also excluded. Suppuration secondary to bronchial neoplasm and suppurative pneumonia in a bronchiectatic lobe likewise were not included. Cases of abscess or suppurative pneumonia preceded by an initially nonsuppurative pneumonia were not included but were placed in the pneumonia series.

In judging whether pneumonia was initially suppurative and whether an abscess was the result of primary rather than secondary suppuration, we were guided largely by the symptomatology and rapidity of onset of roentgenographic and clinical findings suggestive of suppurative disease (excavation, fetid sputum). In the aputrid suppurations we were guided as well by the absence of pneumococci, the presence of a multiplicity of organisms and the subsequent protracted course. Postmortem examination verified the diagnosis in a number of cases, though of course it gave no information regarding the onset.

The patients varied in age from eighteen to seventy-one, most of the group being in the fifth decade. The male sex predominated. Oral sepsis and aspiration during alcoholic stupor were the most frequent aetiological factors responsible for suppuration, with surgery under general anaesthesia, trauma of the neck, disturbances of swallowing and submersion contributing to a smaller number. In one case suppuration was caused by aspiration of a foreign body.

As in the pneumonia series we grouped the cases into the four categories of activation, with an additional category of "suspected superinfection." This grouping, as in the previous series, is based on subjective impressions, guided by certain arbitrary criteria.

The category of "definite activation" includes cases (*1*) in which there was postmortem evidence of a recently activated lesion with recent spread, and (*2*) in which progressive tuberculosis developed, the tuberculosis having previously been stationary, latent or unsuspected. To the category of "probable activation" were assigned cases (*1*) of previously active disease showing signs of progression, clinically or postmortem, (*2*) previously inactive tuberculosis showing signs of activity, though not of progression, (*3*) progressive tuberculosis in the presence of healing of the abscess. The "doubtful" group includes only one case in which death occurred too soon to evaluate the effect of the suppuration in the absence of postmortem examination. A case was considered not to have been activated when a preëxisting tuberculous lesion showed no change clinically

or radiologically. The group of "possible superinfection" includes 6 cases in which tuberculosis developed in the site of a previous abscess from ten months to ten years after onset. There was an intervening period of chronicity of the abscess of at least six months, and the cases showed no clinical or radiological evidence of preceding tuberculosis. However, the possibility of erosion of a microscopical tubercle must not be overlooked and cannot be denied.

Table 6 shows the number of cases in each category. It is noteworthy that 38 of 49 cases showed some degree of activation, while 6 other cases showed progressive tuberculosis based on suspected superinfection. These figures bear comparison with the distribution in the pneumonia series and certainly give

TABLE 6

Activation of tuberculosis by pulmonary abscess

Definite	28
Probable	10
Doubtful	1
None	10
Questionable superinfection	6
Total	55

TABLE 7

Consequences of associated pulmonary suppuration and tuberculosis

Tuberculosis previously recognized	16
Definite or probable activation	9
Tuberculosis present but not previously recognized:	
a. Roentgenographic evidence of old primary complex	3
Definite or probable activation	3
b. Roentgenographic evidence of postprimary haematogenous tuberculosis	4
Definite or probable activation	3
c. Roentgenographic evidence of latent tuberculosis of reinfection type	13
Definite or probable activation	10
No evidence of previous tuberculosis	29
Definite or probable activation	13
Questionable superinfection	6

evidence that suppurative lesions are extremely likely to activate pulmonary tuberculosis.

In table 7 we have grouped the cases in accordance with clinical and radiological evidence of preceding tuberculosis. The table is self-explanatory but attention is called to the 7 cases of calcified primary complex and postprimary haematogenous dissemination, 6 of which showed activation.

Table 8 shows the relationship of the site of the abscess to the site of the tuberculous process, either present before suppuration set in, or developing in the course of the suppurative disease. The conclusion that in the majority of cases local destruction was responsible for activation of the tuberculosis seems inescapable. Twenty-eight of 37 activated cases showed the tuberculosis in the

area of abscess. Only 4 of 32 cases in which suppuration and tuberculosis were localized in the same area showed no activation.

Charts 3 and 4 show the frequency distribution of maximal leucocyte counts and percentages of polymorphonuclear neutrophils. Three-fifths of the cases had counts above 14,000,the mean being in the 14,000 to 18,000 group. The polymorphonuclear percentage curve is skew toward the higher percentages, the largest number of cases showing a percentage between 84 and 89. These figures are, we believe, representative of the effect of suppuration rather than of tuberculosis.

Forty-five patients produced foul sputum at some time during the course of their pulmonary suppuration. Other outstanding symptoms were pleural pain, present in 30 cases, haemoptysis in 20 cases, chill in 19 cases and herpes labialis in 5 cases.

In an analysis of the type of tuberculosis resulting from activation, of 44 cases 20 showed an exudative and caseocavernous issue, 20 had fibrocavernous lesions,

TABLE 8

Topographic relations of pulmonary abscess and tuberculosis

Activation (definite and probable)	
Suppuration in area of tuberculous disease	29
Suppuration not in area of tuberculous disease	9
No activation (doubtful and none)	
Suppuration in area of tuberculous disease	3
Suppuration not in area of tuberculous disease	8

Questionable superinfection—All (6) cases—tuberculosis in area of previous abscess.

while 4 cases showed productive and fibroid disease. One of the latter occurred in an area of organizing pneumonia of the type described by Schröder.

Of 13 cases receiving surgical drainage of the abscess or of complicating empyema, 7 showed a persistent bronchocutaneous or bronchopleurocutaneous fistula, which in most could be shown to be infected with tubercle bacilli. This is of importance in the decision as to surgical treatment in the presence of the combined lesions.

An attempt to study the relation of the bacterial flora causing suppuration to the tuberculous process met with failure, since there was no ascertainable uniformity or even predominance of any organisms. Strictly anaerobic technique was not always employed in culturing the sputum.

There were no cases with proven or suspected haematogenous generalization of tuberculosis following suppuration. Three cases showed tuberculosis in the mediastinal nodes at postmortem examination. In no instance could we demonstrate clinically or at postmortem examination that we were dealing with gangrene involving the wall of a previously tuberculous cavity, or with secondary infection of such a cavity. Animal inoculation of the sputum was not carried

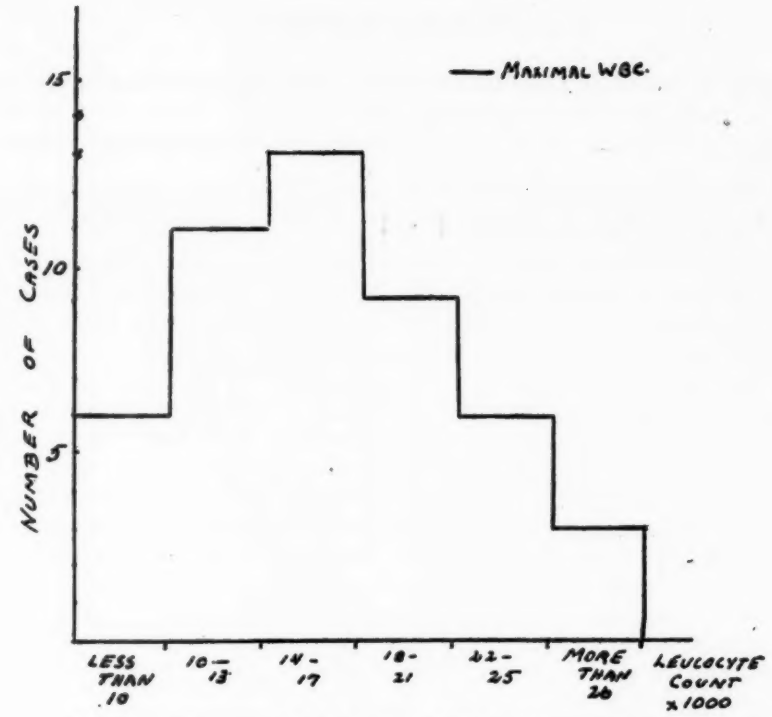

CHART 3. Frequency distribution. Maximal leucocyte counts

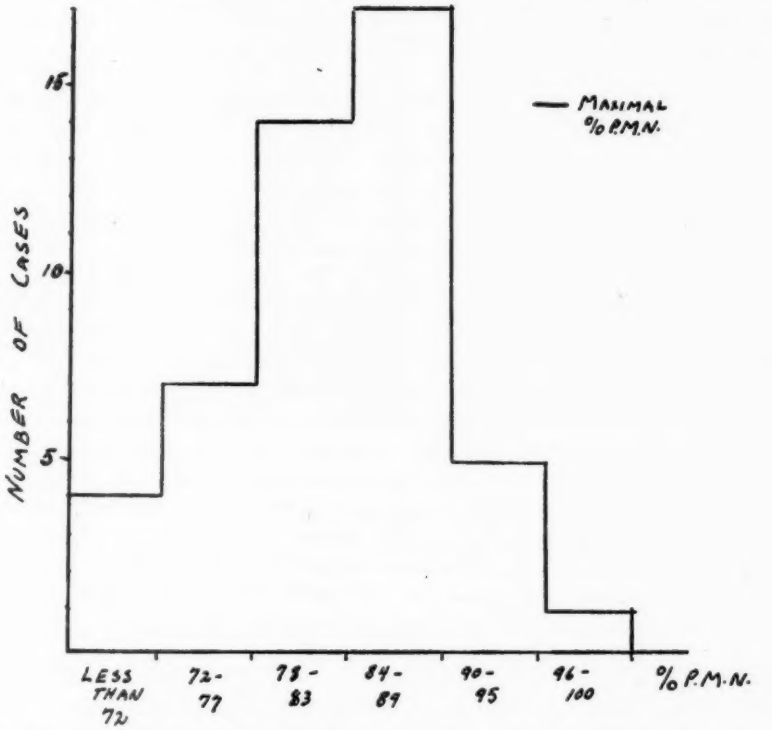

CHART 4. Frequency distribution. Maximal percentage of polymorphonuclear neutrophils

out in any of the cases, since no suspicion existed that acid-fast bacilli demonstrated in the sputum were nonpathogenic.

We have selected the following cases for individual presentation, again from each of the above named categories.

Cases of definite and probable activation:

6. *J. M.:* Male, *aet.* fifty-one, admitted 1933 and 1934. First admission for pneumococcus type-2 pneumonia of right middle and lower lobes, complicating inactive right apical tuberculosis which was not activated. Ten months later, four weeks before second admission, he noted onset of chills, right chest pain, cough productive of four ounces of foul purulent sputum daily. He had two small haemoptyses. On physical examination foul breath was noted. There were increased breath sounds and râles over right upper lobe and apex of right lower lobe. A roentgenogram showed a homogeneous density and fibrosis of right upper lobe, containing a cavity. The horizontal fissure crossed a second cavity in the apex of the right lower lobe. The leucocyte count was 7,800 with 79 per cent polymorphonuclear neutrophils. Sputa were negative for tubercle bacilli for four months, thereafter positive. He had temperature up to 102°F. for two weeks, which thereafter gradually dropped to normal. Bronchoscopy showed foul pus at the mouth of the right upper lobe bronchus which was reddened. Sputum decreased after bronchoscopic aspirations and postural drainage were instituted. He was readmitted six months later showing evidence of rapidly progressive fibrocaseocavernous tuberculosis and laryngeal tuberculosis.

Comment: Case of right upper lobe fibrotic tuberculosis, not activated by pneumococcal pneumonia of right middle and lower lobes, but definitely activated by acute abscess of right upper lobe and apex of right lower lobe.

7. *H. H.:* Male, *aet.* fifty-eight, admitted 1939. Chronic alcoholic, who attempted to commit suicide by jumping into the East River while intoxicated. Admitted to Psychiatric Service where shortly thereafter signs of infiltration at the left base were obtained, and the temperature rose to 103°F., associated with cough productive of bloody sputum. A roentgenogram on the following day showed consolidation of the lower half of the left lung field, with patchy pneumonic densities in the right mid-zone. Just above the area of consolidation on the left there was a calcified tubercle. Sulfapyridine and sulfanilamide were administered despite the absence of pneumococci on typing or haemolytic streptococci, without effect on the course. Rapid progression of the bilateral pneumonic lesion occurred, and elastic fibres were demonstrated in the sputum, which was negative for tubercle bacilli. Six weeks after entry the sputum was first positive for tubercle bacilli, and remained so, while roentgenograms showed coalescent pneumonic areas, as well as nodular areas scattered bilaterally. Laboratory findings showed an initial leucocyte count of 8,900 with 90 per cent polymorphonuclear neutrophils, rising to 24,600 with 92 per cent polynuclears, then dropping to 7,300 with 82 per cent polynuclears. Sputum culture showed *Staphylococcus aureus, Streptococcus alpha* and unidentified gram-positive and negative cocci. Blood culture was negative. The course was progressively downhill, temperature ranging between 101° and 103°F., and the patient died two months after admission. Permission for postmortem examination was refused.

Comment: Case of suppurative pneumonia, following submersion, with definite activation of tuberculosis, probably by erosion of a calcified tubercle.

8. *B. C.:* Male, *aet.* fifty-two, 1940. He entered in diabetic ketosis, having vomited occasionally before entry. Treatment of diabetes included gavages of glucose and sodium bicarbonate. During a subsequent hypoglycaemic episode he bit a glass tube through

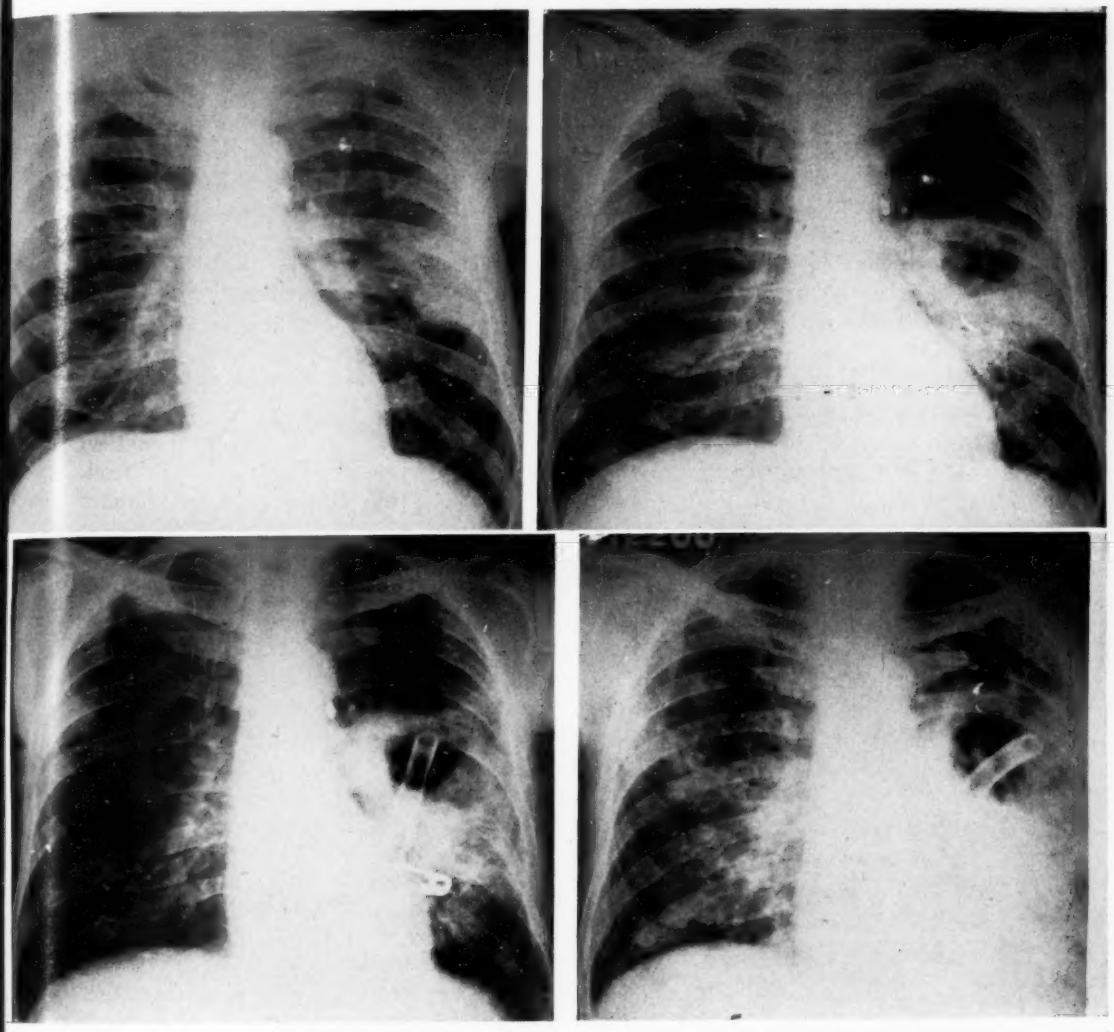

FIG. 9 (upper left). Case 8. June 27, 1940. Admission film. Note area of bronchopneumonia in left fourth anterior interspace, lateral to Ghon tubercle.

FIG. 10 (upper right). Case 8. July 13, 1940. Size of abscess prior to drainage.

FIG. 11 (lower left). Case 8. August 1, 1940. Drainage tube *in situ.*

FIG. 12 (lower right). Case 8. September 3, 1940. Last film prior to death. Note homolateral and contralateral spread.

which he was given orange juice, but all pieces of glass were allegedly recovered. There were no chest signs at entry. During the first week there was unexplained fever up to 101.8°F., and a roentgenogram three days after admission showed a patch of pneumonic

density anteriorly at a level between the third and fifth ribs on the left, adjacent to an area of calcification (figure 9). There were also calcified nodes at the left hilum. During the subsequent two weeks, temperature rose to 104°F., the sputum became foul, and roentgenograms showed multiple areas of cavitation which rapidly merged (figure 10). Leucocyte count was 11,200 with 52 per cent polymorphonuclear neutrophils; it rose to 14,700 with 73 per cent polynuclears. Sputa were negative for tubercle bacilli for two months, thereafter positive. Culture of sputum and of the abscess at operation showed an anaerobic streptococcus. Thoracotomy was performed three weeks after entry but the patient's temperature continued to spike daily to 104°F. On the day following operation, a roentgenogram showed contralateral nodular densities (figure 11). The sputum remained negative until five weeks after thoracotomy, when positive specimens were obtained on direct examination, as well as on examination of a specimen aspirated through the bronchoscope from the opposite lung (figure 12). The cavity remained open and tubercle bacilli were found in the drainage from the wound. The patient died ten weeks after entry. No autopsy was done.

Comment: Case of acute lung abscess, eroding a calcified focus or deposits in the interfocal zone, with extensive tuberculous spread.

Case of suspected superinfection:

9. *C. D.:* Male, *aet.* twenty-three, admitted 1934 and 1935. Past history of asthma, sinusitis, pneumonia at two years of age. Roentgenogram September, 1934 was negative. Shortly thereafter he noted sudden onset of fever, left chest pain and cough productive of eight ounces of foul sputum daily. Physical examination revealed postnasal purulent discharge. There was dulness in left second anterior interspace with few râles. A roentgenogram showed an area of pneumonic density in base of left upper lobe, with a 6 cm. central cavity. Leucocyte count of 17,300 with 80 per cent polymorphonuclear neutrophils dropped to 14,000 with 71 per cent polynuclears and then to 7,400 with 59 per cent polynuclears. Sputum was repeatedly negative for tubercle bacilli. Culture of sputum showed streptococci and staphylococci. Temperature ranged from 100° to 104°F., and the sputum was foul. Following institution of postural drainage the sputum lost its foul character and roentgenogram showed clearing of pneumonia, leaving a residual thin-walled cavity 4 cm. in diameter. Bronchoscopy was negative. Patient was discharged eight months after onset of symptoms, essentially asymptomatic.

Two months after discharge he caught cold and developed a cough productive of up to two ounces of nonfoul sputum daily, fatigue, night sweats, and he lost thirty pounds. On admission, seven months after discharge, a roentgenogram showed a large thick-walled cavity in the region of the preceding abscess, containing a fluid level, with adjacent exudative foci. Sputum was positive for tubercle bacilli, but was converted after institution of pneumothorax, even though the lung was adherent in the area overlying the previous abscess. The contrast of the roentgenograms during the period of suppuration and at the second admission was striking, and together with absence of tubercle bacilli suggests a late onset of tuberculosis.

Comment: Case of suspected superinfection by tubercle bacilli of a residual lung abscess ten months after onset of the latter, and at least six months after chronicity of the abscess was noted.

Case without activation:

10. *M. M.:* Male, *aet.* twenty-six, admitted 1931. Known tuberculosis for nine years, treated at sanatoria for seven years and pronounced arrested. Acute onset two weeks before entry with fever, sweats, weakness, left chest pain, foul sputum. Physical examination revealed fine râles at right apex, harsh breath sounds and medium moist râles above third rib and fourth vertebral spine on the left. A roentgenogram showed fibrotic tuberculous lesion above second rib on right; fibrocalcific deposits in left apex, obscured somewhat by a homogeneous density with a central cavity, containing a fluid level, above the fourth rib. Repeated sputum concentrates were negative for tubercle bacilli. On postural drainage, sputum decreased and lost its fetid character. Roentgenograms showed gradual clearing of the suppurative lesion, leaving the residual fibrocalcific lesion unchanged.

Comment: Case of acute lung abscess in area of fibrocalcific tuberculosis. No activation.

Discussion

We believe that our data support the contention of Ameuille, Léon-Kindberg and others that activation of a tuberculous lesion by a suppurative process depends primarily on direct invasion by the acute necrosis and destruction of the capsule of the tubercle, if any exists. This is particularly warranted, since there are very few reports in the literature regarding breakdown of a healed primary tubercle or of tubercles in the interfocal zone. There are 3 such cases in our series. The fact that the majority of activated cases showed tuberculosis and suppuration in the same area further supports the theory of local destruction.

Our data certainly argue against the contention of Courcoux and Lelong that the two diseases follow an independent course. In only 10 of the 54 cases was this observed, while activation of tuberculosis was conspicuous in 38. The suggestion that superinfection may occur, and the fact that in a number of the cases the abscess cavity was converted into a tuberculous cavity, which remained open, give evidence of a decided effect of tuberculosis on a suppurative lesion.

Thirteen of the cases showed no evidence clinically or radiographically of previous tuberculosis, yet all showed evidence of tuberculosis beginning during the destructive phase of the abscess. This points to the need for careful sputum studies in all cases of pulmonary suppurative disease.

We may conclude that the coexistence of tuberculous and suppurative lesions is not rarely encountered and that in the majority of such instances the course of the tuberculous disease is adversely affected.

BRONCHIECTASIS AND TUBERCULOSIS

Most reports in the literature dealing with the coexistence of tuberculosis and bronchiectasis are concerned with the subject of bronchiectasis resulting from and at the site of a preceding tuberculous lesion. There are extremely few

reports dealing with bronchiectasis arising independently of tuberculosis. It is this subject which concerns us here.

The pathogenesis of bronchiectasis has been well described by many authors and need not enter into this discussion. There are isolated reports in which an indirect connection between the two diseases has been shown, which we would like briefly to mention.

Buhl in 1872 (quoted by Fränkel in 1907 (1)) describes instances of bronchial dilatation and suppurative peribronchitis resulting from phlegmonous undermining of the bronchial mucosa, apparently resulting from secondary infection of the tuberculous mucosal ulcers. The bronchial lesion may go on to suppurative bronchiectasis, while the tuberculous process abates.

Ameuille and Perreau (79) describe 6 cases of bronchiectasis in tuberculous patients, which, they believed, developed as a result of thrombotic occlusion of the bronchial arteries leading to the affected lobe, and based on obliterative endarteritis. The origin of the latter could in one case be traced to a point of contact with a tuberculous bronchopulmonary lymph node. This is a mechanism whereby bronchiectasis may be established in childhood by a tuberculous focus which becomes latent. Subsequent apical tuberculosis in later life may result from activation of postprimary haematogenous foci, whose point of origin was also the factor responsible for the bronchiectasis.

Cournand and Jones (80) discuss another mechanism which may eventuate similarly. They refer to the bronchostenosis and bronchial inflammation consequent to tuberculosis of the bronchopulmonary lymph nodes in children, particularly of those surrounding the right middle lobe bronchus. Distal to such stenosis a suppurative process may occur, causing destruction of the bronchi as well as of the parenchyma, and the end result is usually a bronchiectatic shrunken lobe.

Fränkel (1), Schröder (3) and Simon (81) mention that tuberculosis may supervene in a preceding bronchiectasis. The latter authors insist on the importance of distinguishing between true tubercle bacilli and saprophytic acid-fast rods inhabiting the bronchiectatic cavities. Simon reported a number of cases in which cultural studies and animal inoculation proved the character and pathogenicity of the acid-fast bacilli. The presence of bronchiectasis was proved by lipiodol studies. Eight of his cases were children between the ages of three and fourteen.

Morse and Shinn (82) in a general discussion of bronchiectasis describe one case showing both lesions, the bronchiectasis being discovered after collapse therapy had rendered the sputum negative, but failed to decrease the amount of sputum.

Bray (83) describes a case of bronchiectasis, observed for seven years during which time the sputum was negative for tubercle bacilli. The tuberculin test was positive at the time when the patient was first seen. During the eighth year tubercle bacilli were demonstrated and the patient died of extensive pulmonary and haematogenous tuberculosis. Whether this was an exacerbation of a latent tuberculous lesion at puberty, or a superinfection of bronchiectatic cavities during the repeated sanatorium admissions cannot be decided with certainty.

Analysis of Data

Our series is composed of 32 cases treated on the wards of the Tuberculosis Service between 1929 and 1941. Charts and roentgenograms of all cases discharged with the combined diagnosis were examined, and all cases of known and suspected posttuberculous bronchiectasis were excluded from the series. Also excluded were cases of bronchiectasis secondary to tuberculous bronchostenosis. The cases range in age from seventeen to seventy-four, the majority being below the age of forty.

In all but 3 cases was the diagnosis of bronchiectasis proved by bronchography. In 3 cases the diagnosis was strongly suspected because of the persistence of coarse basal râles and continuation of symptoms, such as profuse purulent sputum, in the absence of radiological evidence of parenchymal disease. The nature of the bronchiectasis was saccular and cylindrical in 13 cases, saccular in 8, cylindrical in 3 and cystiform in 2. Three cases showed bronchiolectasis, one of them seen in conjunction with saccular bronchiectasis of another lobe.

In the majority of cases symptoms of bronchiectasis dated to childhood and occurred subsequent to measles, pertussis or other pneumonias unrelated to preceding infectious diseases. A smaller number resulted from pulmonary suppuration occurring during adult life.

The outstanding symptoms of bronchiectasis were haemoptysis, seen in 22 cases, foul sputum in 14 cases and copious nonfoul sputum in 9 cases.

This group of cases does not lend itself to analysis by the methods utilized in the analysis of the previous groups. This is so because the number of cases is relatively small, and because adequate criteria of activation of tuberculosis cannot be set up, since bronchiectasis preceded the onset of tuberculosis usually by a number of years. However, certain interesting findings may be discussed.

In 13 of the 32 cases there was definite evidence that tuberculosis was superimposed on a preceding bronchiectasis. In other words, in these cases at the time when the diagnosis of bronchiectasis was made there was no clinical or roentgenological evidence of tuberculosis. In 7 of these cases tuberculosis developed in a bronchiectatic lobe, while in 6 it developed in a lobe shown to be uninvolved by bronchiectasis.

In the entire group tuberculosis was located in a bronchiectatic lobe in 9 cases, in an uninvolved lobe in 23 cases.

Suppurative pneumonia or persistent suppurative bronchiectasis occurred in 14 cases, 9 of which showed progressive tuberculosis. These were absent in 18 cases, 6 of which showed progressive tuberculosis.

A few comments about treatment are in order. Lobectomy of the bronchiectatic lobe was performed in 4 cases, all of which were actively suppurating, and in which attempts at preoperative reduction of the amount of sputum by postural and bronchoscopic drainage met with little success. All of these developed postoperative empyema, which in 2 was also infected with tubercle bacilli. These 2 cases also showed progression of parenchymal tuberculosis.

Tuberculosis was treated by artificial pneumothorax in 4 cases and by thoracoplasty in 3, 2 of which had empyema. The tuberculosis was arrested in 5 of

the 7 cases. In one case of pneumothorax converted to an oléothorax, and in a case of thoracoplasty the tuberculosis remained active. In all instances collapse therapy had no effect on the symptoms of bronchiectasis.

One case refused lobectomy and was treated at another institution with roentgen therapy. This was followed by rapid progression of the tuberculosis to a fatal termination.

The following cases have been selected for detailed presentation.

11. *T. McG.:* Male, *aet.* thirty, admitted 1929 and 1933. Fourteen months before entry he developed suppurative pneumonia of the left lung, followed by the development of fibrothorax and the demonstration of saccular bronchiectasis. He was hospitalized for a brief period at a tuberculosis sanatorium, where sputum examinations were negative for tubercle bacilli. Roentgenograms preceding the pneumonia had shown no evidence of parenchymal disease. His cough was productive of sixteen ounces of nonfoul sputum daily. He had clubbing of fingers and toes. There were signs of left fibrothorax with bronchial breath sounds and coarse râles throughout the left lung. The right lung was clear. A roentgenogram revealed a left fibrothorax and emphysema of the right lung. Bronchography demonstrated saccular bronchiectasis of the left upper and lower lobes. Leucocyte count was 14,800 with 86 per cent polymorphonuclear neutrophils. Sputum was positive for tubercle bacilli. Following defervescence of fever, a left phrenicoexairesis was done, followed by a ten-rib thoracoplasty. Since the sputum remained positive for tubercle bacilli, a revision of the thoracoplasty was done, resulting in conversion of the sputum which remained negative until death. There was no change in the symptoms of bronchiectasis. During an admission for these symptoms, eighteen months after conversion of the sputum, he developed a chill, his temperature rose to 105°F., his leucocyte count from 13,650 with 87 per cent polymorphonuclear neutrophils to 20,000 with 89 per cent polynuclears, and he suddenly expectorated a large amount of nonfoul sputum. Roentgenogram showed an abscess of the right middle lobe. The sputum rapidly became foul and preparations for surgical drainage were made. However, the patient suddenly became dyspnoeic and expired. Postmortem roentgenogram showed a spontaneous pneumothorax on the right, resulting undoubtedly from perforation of the abscess into the pleura.

Comment: Case of suppurative pneumonia and bronchiectasis, followed by tuberculosis treated successfully with thoracoplasty. Death occurred following rupture of an abscess of the opposite lung into the pleura. The source of this abscess was most likely the continuing suppurative bronchiectasis.

12. *R. K.:* Male, *aet.* twenty-one, admitted 1933 and 1937. History of productive cough since childhood. Two months before entry he had a haemoptysis, and two weeks before entry he was acutely ill with cough, foul sputum and fever. On admission there were signs of consolidation and effusion on the left. Leucocyte count was 28,000 with 82 per cent polymorphonuclear neutrophils. Sputa were repeatedly negative. Thoracocentesis yielded foul creamy pus, and gentian violet installation demonstrated the presence of bronchopleural fistula. Following surgical drainage and closure of the fistula, bronchography demonstrated bronchiectasis of the left lower lobe and lingula of the left upper lobes (figure 13). During subsequent admissions for acute pneumonia of the left lower lobe sputa were negative (figure 14). Two years after the first admission sputum was first found positive, and at this time fine nodular lesions were present in

the right midlung field (figure 15). Several months later a two-stage thoracoplasty was done, and the sputum turned negative. Postoperative bronchograms showed no change. Five months after completion of the thoracoplasty the sputum was again positive after several severe haemoptyses. The patient showed extensive contralateral spread of the tuberculosis and died following a sudden onset of convulsions, thought to be caused by brain abscess.

Comment: Case of unilateral bronchiectasis and suppurative pneumonia, with supervening tuberculosis, whose progression was not checked by thoracoplasty. Death due probably to brain abscess.

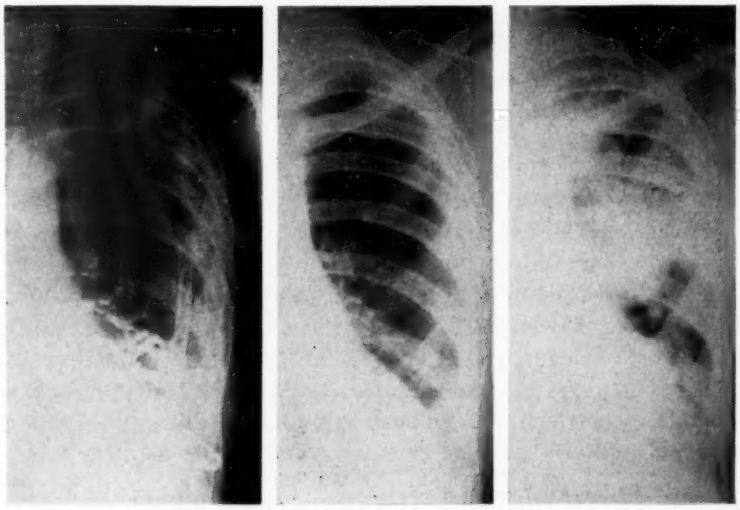

FIG. 13 (left). Case 12. March 23, 1933. Drainage tube in empyema cavity. Bronchogram of left lower lobe.

FIG. 14 (center). Case 12. December 28, 1933. After closure of empyema space.

FIG. 15 (right). Case 12. April 13, 1935. Extent of tuberculosis prior to thoracoplasty.

13. *A. F.:* Male, *aet.* twenty-five, admitted 1939–1941. History of cough productive of purulent sputum since childhood. Six weeks before entry he had haemoptysis followed by increasingly foul sputum. On physical examination he showed clubbing of fingers, dental caries and pyorrhoea. There were dulness, diminished bronchovesicular breath sound and many moist râles below the seventh vertebral spine on the left. A roentgenogram showed a bilateral apical productive lesion, more extensive on left, and a dense pneumonic lesion with several highlights in the left lower lung field. The leucocyte count varied between 7,500 and 18,750 with a percentage of polymorphonuclear neutrophils between 65 and 88. Sputum was negative for tubercle bacilli for seven months, thereafter positive. Sputum culture yielded anaerobic streptococcus and few Friedlander bacilli. He was treated with postural drainage and bronchoscopic aspirations and, after four months of such preparatory treatment and preliminary pneumothorax, lobectomy of the left lower lobe was performed. The lobe showed saccular and cylindrical bronchiectasis and suppurative pneumonia. A fistula of the bronchial stump developed and foul empyema which was drained. Three months after lobectomy the

sputum was first found to be positive, and two months later tubercle bacilli were found in the wound fluid. The patient since then has had three stages of a left thoracoplasty and implantation of muscle into the empyema cavity. At the time of writing, his sputum is still positive.

Comment: Case of unilateral bronchiectasis and suppurative pneumonia with coexisting bilateral apical tuberculosis, and breakdown of the homolateral tuberculosis, probably due to extension of suppuration following lobectomy, bronchopleural fistula and empyema. Three stages of thoracoplasty have so far failed to render the sputum negative.

Discussion

We are unable to draw any definite conclusions regarding the coexistence of bronchiectasis and tuberculosis, but have certain impressions which warrant discussion.

It must be granted that an ultimate coexistence of these two apparently unrelated diseases may be based on changes resulting primarily from tuberculosis. Bronchiectasis may result, as discussed above, following a childhood tuberculous infection of bronchopulmonary lymph nodes. Subsequent parenchymal tuberculosis in later life may be an exacerbation of postprimary apical haematogenous foci, which were established concurrently with the bronchiectasis.

In most cases, however, the origins of the two diseases are separate. The incidence of tuberculosis in cases of bronchiectasis seems no greater than in the general population. Once it develops, it is probably more likely to progress, because of the greater chance of dissemination by the copious bronchial discharges, as well as by haemorrhage which so frequently is seen in bronchiectasis. The presence of suppuration seems definitely to favor the progession of tuberculous lesions, particularly if the latter become established in the bronchiectatic lobe. Collapse therapy is of value in treatment of the tuberculosis, but has little or no effect on the coexisting bronchiectasis; the effect may be deleterious in the presence of suppuration, leading to empyema. Lobectomy is the treatment of choice of bronchiectasis, though tuberculosis may be activated by overexpansion of the lobe containing this lesion to fill the space of the resected lobe. Transbronchial drainage of the products of suppuration, particularly if bronchopleural fistula and empyema supervene, may result in such activation either before or after lobectomy.

SUMMARY AND CONCLUSIONS

1. We have presented 102 cases of pneumonia in 97 tuberculous patients, 55 cases of lung abscess and suppurative pneumonia occurring in 54 patients ultimately showing tuberculosis, and 32 cases of coexisting bronchiectasis and tuberculosis.

2. Pneumonia is not rare in the tuberculous population and when present has potentialities of activating a tuberculous lesion.

3. Suppuration within a pneumonic area is the most important factor in subsequent activation of a tuberculous lesion.

4. Such suppuration not infrequently complicates pneumonia caused by type-3 pneumonococci and is usually present to some degree in infections caused by haemolytic streptococci and other invaders of the interstitial tissue.

5. Bronchorrhoea and local hyperaemia are factors which also may play an important rôle in activation of a tuberculous lesion by pneumonia.

6. Fibrocalcific lesions and lesions successfully controlled by collapse therapy are least likely to be activated by pneumonia.

7. Suppurative pulmonary lesions, such as lung abscess, gangrene and initially suppurative pneumonia not infrequently coexist with pulmonary tuberculosis.

8. The course of pulmonary tuberculosis is usually affected adversely by complicating nontuberculous suppurative lesions.

9. Tuberculosis may become implanted on preëxisting suppurative lesions and on bronchiectasis.

10. Activation of tuberculosis by suppurative disease is in the majority of cases dependent on local destructive processes, resulting in disruption of the capsule, if any, and breaking down of the tuberculous focus.

11. Tuberculosis, once developing in cases of bronchiectasis, is likely to progress, being disseminated by copious purulent discharges and haemorrhage, but may be arrested by collapse therapy.

12. The presence of suppuration in bronchiectasis favors progression of tuberculosis, particularly if the latter becomes established in a bronchiectatic lobe.

SUMARIO Y CONCLUSIONES

1. Preséntanse 102 casos de neumonía en 97 tuberculosos, 55 casos de absceso pulmonar y neumonía supurada en 54 enfermos que revelaron ulteriormente tuberculosis, y 32 casos de bronquiectasia coexistente con tuberculosis.

2. La neumonía no es rara entre los tuberculosos, y cuando existe posee potencialmente la facultad de activar una lesión tuberculosa.

3. La supuración en una zona neumónica constituye el factor más importante en la activación subsecuente de una lesión tuberculosa.

4. Esa supuración complica bastantes veces la neumonía provocada por los neumococos de tipo 3 y suele presentarse hasta cierto punto en las infecciones ocasionadas por estreptococos hemolíticos y otros invasores del tejido intersticial.

5. La broncorrea y la hiperemia local son factores que también pueden desempeñar un papel importante en la activación por la neumonía de una lesión tuberculosa.

6. Las lesiones fibrocalcificadas y las cohibidas eficazmente por la colapsoterapia son las menos susceptibles de reactivación por la neumonía.

7. Bastantes veces coexisten con la tuberculosis pulmonar lesiones pulmonares supuradas, tales como absceso, gangrena y neumonía inicialmente supurada.

8. La evolución de la tuberculosis pulmonar suele ser afectada adversamente por la existencia de lesiones supuradas no tuberculosas como complicación.

9. La tuberculosis puede implantarse en las lesiones supuradas preexistentes y en la bronquiectasia.

10. La activación de la tuberculosis por una afección supurada depende en la mayoría de los casos de procesos destructores locales, que rompen la cápsula, si la hay, y desintegran el foco tuberculoso.

11. Una vez que se presenta en casos de bronquiectasia, la tuberculosis probablemente seguirá avanzando, diseminándola las abundantes secreciones purulentas y las hemorragias, pero puede cohibirla la colapsoterapia.

12. La existencia de supuración en la bronquiectasia favorece el avance de la tuberculosis, en particular si la última se establece en un lóbulo bronquiectático.

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TUBERCULOSIS IN OLD AGE[1, 2]

ARTHUR REST

The literature is controversial in its description of pulmonary tuberculosis in the aged. Collis (1) is of the opinion that senile phthisis is distinctive in its clinical and anatomical manifestations from the disease in the earlier periods of life. Landis (2), Shuman (3) and Schlesinger (4) describe it as a relatively benign form of pulmonary tuberculosis. Still others assume an opposite view. Taubert (5) refers to senile phthisis as a rapidly progressive and fulminating type of tuberculosis. There is little unanimity of opinion regarding tuberculosis in the aged. It is my endeavor to present an analysis of the features of senile phthisis in a group of patients, fifty-five years of age and over, and to derive from this study certain substantial conclusions.

In the selection of my material, the acceptance of the chronological definition of old age was a problem. Pinner (6) in an editorial mentions, in an analogy, that "the first evidences of senility begin long before the third decade of life is completed. This may be correct for practical application but must be scrutinized as to its scientific accuracy and pragmatic value as well." The determination as to the time when evolution passes into involution of the body is indeed difficult.

Nordmeyer (7) chose forty-five years when old age first becomes manifest. Godwin (8) described senile tuberculosis in persons over fifty. Weise (9) used sixty years as his starting point of investigation. Tuberculosis is predominantly a disease of early adult life, and I have chosen fifty-five years as the beginning of tuberculosis in the aged. This is accepted by me as the time of life when bodily changes altering the manifestations and course of disease probably become evident. The aforementioned classifications are arbitrary. Social-economic conditions, deprivation and habits of life are important factors in producing physiological and anatomical changes that characterize old age. Perhaps in the future science will determine a method of classifying old age according to certain classical body changes rather than to measure old age in years.

The changes which especially counteract the spread of tuberculosis in the aged are believed to be the decreasing tendency of aging tissues to become susceptible to inflammatory processes and the increasing tendency for the development of fibrous tissue. An important added factor is obliteration of the lymphatic channels. With advanced age, it is a natural process of the body to undergo certain involutional changes that might render it resistant to the evanescence and spread of tuberculosis. On the other hand, with advanced

[1] From the Medical Department of the Sanatorium of the Jewish Consumptives' Relief Society, Spivak, Colorado.

[2] Presented at the combined meeting of the Colorado Tuberculosis Association and the Denver Sanatorium Asscciation, Denver, Colorado, February 20, 1941.

age, there is concomitant atrophy, decalcification and dehydration of tissue. In the course of deterioration, is it not possible for the calcium of a healed lesion, deposited in earlier life to become absorbed in later life? Might not this absorption be a factor in renewed activity? Sweany (10) states that "judging from the presence of live bacilli obtained from calcified and ossified foci, it is entirely possible that nature may defeat her own purpose in the resorption of the walls of the old tubercles."

The autopsy findings relative to the frequency of tuberculosis in the aged vary. Andrews (11) reviewed the necropsy records of 109 aged persons. Thirteen whose ages averaged over sixty-six years had evidences of pulmonary tuberculosis. Twelve had healed lesions and only one, or less than 1 per cent of the 109, had active tuberculosis. Proescher (12) studied the autopsy records of 750 people from ages sixty to ninety-eight. One hundred and twenty-four showed tuberculous findings. Only 26, or one-third of 1 per cent, had active lesions. Among 1,800 autopsies in people over sixty, Schlesinger (4) found that 501 cases (28 per cent) had old and recent tuberculosis.

The Census Bureau (13) reports that there has been a large increase in people sixty-five years of age or older. The phthisiologist is aware that tuberculous individuals live longer and that the mortality has taken a downward trend. The Metropolitan Life Insurance Bulletin of 1938 (14) illustrates this noticeable change very well. Overholt (15) mentions that the average age of the sanatorium population has increased and a third of the patients are over forty years of age. At the Sanatorium of the Jewish Consumptives' Relief Society, we discourage the admission of patients in the advanced years of life. Consequently, no true determination can be made. However, in the past few years there has been a steady increase in applications for admission of elderly people with active tuberculosis. From 1921 to 1941, 142 patients fifty-five years of age and over were admitted to this sanatorium. Their ages varied from fifty-five to seventy-four upon admission and fifty-five to ninety at death. The duration of tuberculosis ranged from less than one year to forty-five years. The period of residency varied from less than one year to sixteen years. Seventy-four were admitted in the first decade (1921 to 1931) and 68 in the second decade (1931 to 1941). The first decade was of unusual interest in that it followed two events that influenced mankind in general—first, physical: the influenza epidemic; and second, economic: the World War. The second decade witnessed the depression. The course of 165 of the 172 cases was observed through our follow-up system. Seven remained untraceable after discharge. There were 139 males and 13 females.

The majority of cases fell in the fifty-five to sixty-five year group. On the basis of the proportion of the living tuberculous with the living nontuberculous there is no age group after fifty-five that contains so many living tuberculous as that between fifty-five to sixty-five. Only a small proportion of patients survived this age period (table 1).

In the decade 1921 to 1931 only 4, or 6 per cent of cases admitted in that period, are still alive in 1941 (table 2).

Sixty-three, or 85 per cent of the 67 traceable cases, admitted in the 1921 to 1931 period, have died. The 7 nontraceable cases are not included. Table 3 illustrates an analysis of these cases.

Sixty-eight cases were studied in the 1931 to 1941 period. Table 4 represents an analysis of the 37, or 54 per cent, living patients.

An analysis of the 31 or 46 per cent of the dead patients, admitted in the 1931 to 1941 period, is given in table 5.

The onset of the disease was that common to pulmonary tuberculosis at any period of life. Where the onset of symptoms occurred in early adult life, the course was relatively benign. It was characterized by periods of exacerbation alternating with prolonged periods of remission and relatively good health.

TABLE 1

Age groups on admission

1921–1931		1931–1941	
Age	Number	Age	Number
55–60	44 or 59%	55–60	48 or 71%
60–65	14 or 19%	60–65	16 or 23%
65–70	12 or 16%	65–70	4 or 6%
70–75	4 or 6%		

TABLE 2

Patients (admitted 1921–1931) still living in 1941

CLASSIFICATION	TYPE OF LESION	SPUTUM	AGE ON ADMISSION	FOLLOW-UP	DURATION OF TUBERCULOSIS TO 1941 IN YEARS
Far advanced	Cavity—right upper lobe	Negative	55	Curing	38
Moderately advanced	Biapical fibrosis	Negative	58	Curing	22
Moderately advanced	Fibrosis, both upper lobes	Negative	55	Working	15
Far advanced	Cavity—left upper lobe	Negative	55	Working	14

In many cases there was a complete subsidence of symptoms with good working capacity for many years after an initial illness of brief duration. With the approach of the fifth decade and thereafter, exacerbations become more frequent with distinct evidence of progression. It was demonstrated that where tuberculosis first became manifest in later life, the disease was rapidly progressive to a fatal termination in the majority of cases. Resistance to tuberculosis is decreased rather than increased in old age. The immunity acquired in earlier years of life plays the most important role in the chronic course of the disease. In many cases that gave a history of recent onset, the character of the lesion left little doubt that the origin of tuberculosis was years and even decades before the age of fifty-five. The lesion was the unusually benign type throughout the earlier years of life. The pathology of pulmonary tuberculosis in the aged differs in no detail from that of tuberculosis in the earlier periods of life.

TABLE 3

Dead—63 or 85 per cent

1921–1931

History of Onset

1918–1919 (influenza epidemic) 24 or 32 per cent

Classification:	
Far advanced	53 or 84%
Moderately advanced	9 or 14%
Minimal	1 or 2%
Type of lesion:	
Fibroulcerative and caseous pneumonic	42 or 67%
Fibroid	21 or 33%
Complications:	
Laryngeal	10 or 19%
Renal	3 or 5%
Enteritis	4 or 6%
Genital	2 or 4%
Addison's disease	1 or 2%
Complications—nontuberculous:	
Cardiovascular-renal	12 or 19%
Diabetes	2 or 4%
Complications—nontuberculous (Continued):	
Cerebral haemorrhage	3 or 5%
Cancer of rectum	1 or 2%
Nontuberculous broncho-pneumonia	1 or 2%
Skull fracture	1 or 2%
Sputum:	
Positive	53 or 84%
Negative	10 or 16%
Duration of Tuberculosis to Death:	
1– 5 years	40 or 64%
5–10 years	2 or 3%
10–20 years	10 or 15%
20–30 years	6 or 10%
30–40 years	3 or 5%
40–45 years	2 or 3%

TABLE 4

Living—37 or 54 per cent

1931–1941

Classification:	
Far advanced	28 or 75%
Moderately advanced	8 or 22%
Minimal	1 or 3%
Type of lesion:	
Fibroulcerative	19 or 51%
Fibrotic	18 or 49%
Sputum:	
Positive	21 or 57%
Negative	16 or 43%
Complications—tuberculous:	
Renal	1 or 3%
Complications—nontuberculous:	
Cardiac	2 or 6%
Diabetes	1 or 3%
Bronchial asthma	1 or 3%
Buerger's disease	1 or 3%
Cystitis	1 or 3%
Collapse therapy:	
Thoracoplasty	1 or 3%
Phrenic exairesis	1 or 3%
Duration of Tuberculosis to 1941	
2–10 years	17 or 46%
10–20 years	11 or 29%
20–30 years	5 or 14%
30–40 years	4 or 11%

However, the pathology of old age has a profound effect on the pathology of tuberculosis and is especially responsible for the high mortality in certain cases. Chronic bronchitis, bronchiectasis, emphysema, cardiovascular-renal

degeneration and the manifestations of senility were common in my cases. These changes altered the course of pulmonary tuberculosis, or were independently responsible for the downward trend of the unfavorable case.

Treatment of tuberculosis in the aged is not very satisfactory. Alexander (16) states that the operative risk is relatively great in patients in late middle life, because of impaired cardio-respiratory reserve. We of the Sanatorium of the Jewish Consumptives' Relief Society feel that thoracic surgery should be restricted rather than extended where older patients are under consideration.

TABLE 5
1931–1941

Died of Tuberculosis	20 or 64%	*Died of Causes Other Than Tuberculosis*	11 or 36%
Within three years of onset of tuberculosis	13 or 65%	Cardiorenal	4 or 37%
After three years from onset of tuberculosis	7 or 35%	Coronary thrombosis	2 or 18%
		Cancer of lungs, liver, stomach, resp.	3 or 27%
Classification:		Myeloid leukaemia	1 or 9%
Far advanced	19 or 95%	Senile gangrene	1 or 9%
Moderately advanced	1 or 5%		
		Classification:	
Type of lesion:		Far advanced	9 or 82%
Caseous-pneumonic and ulcerative	11 or 55%	Moderately advanced	2 or 18%
Fibrotic	9 or 45%	*Type of lesion:*	
		Fibroulcerative	6 or 55%
Sputum:		Fibrotic	5 or 45%
Positive	19 or 95%		
Negative	1 or 5%	*Sputum:*	
		Positive	7 or 65%
Complications—Tuberculous and nontuberculous		Negative	4 or 35%
Laryngitis	3 or 15%	*Duration of Tuberculosis—31 Cases*	
Renal	2 or 10%	3 years or less	13 or 42%
Diabetes	2 or 10%	3–10 years	4 or 13%
		10–20 years	5 or 16%
		20–30 years	9 or 29%

Overholt (15) assumes an opposite view. He believes that an older patient who has good resistance to the infection and is suffering principally from mechanical effects should respond to thoracoplasty as well as, or better than, a younger person whose instability is due to lack of resistance to the infection. He adds that pneumothorax and phrenic nerve surgery are much less apt to be successful in older patients than in younger individuals. Auerbach and Green (17) mention that at the Sea View Hospital, New York City, pneumothorax was attempted in 58 cases of senile tuberculosis; 49 died within two years after induction of pneumothorax. Complications were frequent. Thoraco-

plasty was performed in 13 cases. There was sputum conversion in only one case. It is well recognized that advanced age, together with stiffness of the chest wall, firmness and fixation of the lung, and impaired cardio-respiratory reserve contraindicate collapse therapy.

CONCLUSIONS

1. Tuberculous individuals can live their normal span of life or even exceed the recognized life expectancy.

2. Active tuberculosis in the aged is serious. Few patients proceed to arrest and even with improvement their status is reduced to that of chronic invalidism. Resistance to tuberculosis is decreased rather than increased in old age.

3. The age period between fifty-five and sixty-five is conspicuous in that it contains the largest number of living aged tuberculous. Relatively few patients survive this period of life.

4. There has been a gradual and noticeable increase in morbidity of tuberculosis in the aged.

5. Patients who develop adult tuberculosis after the fifth decade do poorly. Their reaction is of a highly allergic nature. On the other hand, those patients who develop tuberculosis at an early age handle their reactivation in later life much better.

6. There is a certain group of patients whose history of an active pulmonary tuberculosis dates back many years and even decades. They subsequently present the sequelae of an old tuberculous infection, characterized by apical fibrosis, bronchitis, bronchiectasis of the upper lobes and emphysema. Their sputum is persistently negative. These patients usually die from causes other than active tuberculosis.

Consequently, from an anatomical standpoint, senile tuberculosis may be divided into two categories, those who present:

(*1*) The characteristics of adult pulmonary tuberculosis, namely, infiltration, exudation, caseation, cavitation and a combination with fibrosis; sputum is positive. This type is called infectious tuberculosis.

(*2*) Sequelae of a preëxistent active pulmonary lesion, as just described. Sputum is negative. This type may be given the term obsolete tuberculosis.

7. Collapse therapy is unsatisfactory in the aged. However, we must be guided by the physiological age of the patient rather than the chronological age in determining active treatment.

CONCLUSIONES

1. La vida de los tuberculosos puede alcanzar la duración normal, y hasta superar la expectativa reconocida.

2. En las personas de edad la tuberculosis activa resulta grave, y pocos enfermos pasan al estacionamiento, y aun cuando mejoren, quedan reducidos a un

estado de invalidismo crónico. En los viejos la resistencia a la tuberculosis disminuye más bien que aumenta.

3. El período etario de los 55 a los 65 años se destaca por contener el mayor número de tuberculosos vivos de cierta edad, siendo relativamente pocos los que sobreviven ese período de vida.

4. En la morbidad tuberculosa en las personas de edad, ha tenido lugar un aumento gradual notable.

5. Las personas que manifiestan tuberculosis del adulto más allá del quinto decenio de vida lo pasan mal. Su reacción es de una naturaleza muy alérgica. En cambio, los enfermos que manifiestan tuberculosis a una edad temprana resisten mucho mejor la reactivación más tarde en la vida.

6. Existe un grupo de enfermos cuya historia de tuberculosis pulmonar activa se remonta a muchos años y hasta decenios atrás. Más adelante presentan las secuelas de una antigua infección tuberculosa caracterizada por fibrosis apical, bronquitis, bronquiectasia de los lóbulos superiores y enfisema, mientras que el esputo se muestra persistentemente negativo. Estos enfermos mueren por lo general de otras causas distintas de la tuberculosis activa.

Por consiguiente, anatómicamente podemos dividir la tuberculosis senil en dos grupos que presentan:

(1) Las características de la tuberculosis pulmonar del adulto, a saber, infiltración, exudado, caseación, cavernas y combinación con fibrosis y esputo positivo. Este tipo se denomina infeccioso.

(2) Secuelas de una lesión pulmonar activa previa, semejantes a las que se acaban de describir, mas en las que el esputo es negativo. A este tipo podríamos llamarlo tuberculosis antigua.

7. La colapsoterapia no resulta satisfactoria en las personas de edad, pero la edad fisiológica más bien que la cronológica decidirá si conviene o no el tratamiento activo.

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COMPULSORY ISOLATION FOR TUBERCULOSIS[1]

Its Effect on the Spread of Tuberculosis in Contacts during One Decade

P. K. TELFORD AND EMIL BOGEN

Isolation of patients with positive sputum is necessary for the prevention of the spread of tuberculosis (1). Every case institutionalized contributes to this goal (2) but efforts should not cease until every consumptive who endangers others has been effectively segregated.

During the past decade the Los Angeles County Health Department has asserted its legal authority in the control of tuberculosis in an increasing number of instances (3). The first order for isolation was issued May 1, 1931, and the present legal form instituted November 11, 1931. More than 800 contacts or suspects have since been examined under legal orders, and more than 500 patients with active disease have been subjected to compulsory legal isolation in institutions. An even greater number have allowed similar measures without legal orders, as a result of recognition of this authority.

More than 100 arrests and convictions have attended these efforts. The legality of the procedure has been repeatedly asserted by the County Counsel and the State Attorney General, consistently supported by the local courts and, following appeal, by the State courts (4). The policy has been gradually extended, but still needs wider application. It is now limited chiefly by insufficiency of institutional beds and by delay in diagnosis not only of early cases but also of the more important unrecognized advanced cases (table 1).

The effect of compulsory isolation on the spread of tuberculosis has been observed among 493 persons in 87 families of patients so isolated. These household contacts were tuberculin tested, reactors were X-rayed, physical and sputum examinations were made when indicated, and negative tests or X-ray films repeated at least once a year in most instances (table 2).

At the time when these 493 members of exposed families were first examined by the Health Department, 148 gave positive tuberculin reactions and 45 showed active tuberculous lesions. The duration of previous exposure in these cases can only be imagined, but the need for earlier diagnosis to lessen it is obvious.

Between the date of the diagnosis and the issuance of the order for isolation, another 49 positive tuberculin tests and 14 instances of clinical tuberculosis developed among the contacts. This period varied, averaging about one and one-half years. Most of the new cases arose among the contacts with the longer periods of exposure. The delay in breaking the contact is unfortunate. Lack of beds, of coöperation, or of legal or economic qualifications should not have been allowed to obstruct the necessary public health measure.

[1] From Olive View Sanatorium, Olive View, California.

After isolation was effected, there remained 296 contacts who had not yet been infected, 138 who had only a positive tuberculin reaction and 59 who had already developed tuberculous disease. During the ensuing period of observation, averaging more than four and a half years up to January, 1941, 107 more instances of infection and 19 more active cases were detected. This average of about 21 new infections and 4 new instances of disease per year after the

TABLE 1

Forcible measures in tuberculosis control. Los Angeles County

FISCAL YEAR	EXAMINATION ORDERS	ISOLATION ORDERS	THREATS MADE	VIOLATIONS REPORTED	TOTAL
1931	33	30	167	12	242
1932	96	50	181	43	370
1933	81	42	45	29	197
1934	78	22	12	34	146
1935	65	32	3	23	123
1936	99	21	18	16	154
1937	118	70	34	9	231
1938	110	81	34	19	244
1939	129	149	31	14	323
Total.....	809	497	525	199	2,030

TABLE 2

The development of tuberculosis among contacts of 87 patients legally isolated in Los Angeles County 1931–1939 inclusive

	TUBERCULOUS INFECTION ONLY	TUBERCULOUS DISEASE	TOTAL
Before diagnosis of initial case.....	103	45	148
Between diagnosis and isolation.....	35	14	49
During isolation.....	31	11	42
After death of initial case.....	31	7	38
After release from isolation.....	26	1	27
Total positive.....	226	78	304
Still negative.....			189
Total.....			493

imposition of isolation is less than half the corresponding figures for the period between diagnosis and isolation. It is still far too high.

Many of these apparent failures of isolation represent the delayed appearance or progression of infections previously acquired. More than half of all of the infections and lesions found in the contacts after their separation from the primary case were discovered within a year of the time that the isolation order was issued. Others resulted from intermittent or lax enforcement of isolation. There were 42 infections and 11 active cases found during the period of isola-

tion, which averaged about two years. Another 38 new infections, and 7 instances of tuberculous disease, were found in the contacts after the death of the isolated patient. Nearly half of the primary patients died while under isolation, some of them soon after the separation, and the incidence of infection among the contacts of these terminal cases was much higher than among those of the cases who survived.

Nearly half of the patients isolated were finally released, usually after their sputum had become microscopically negative for tubercle bacilli, but in some other instances when children had been removed from the household or other provisions made for the prevention of domestic exposure. In the average of two and a half years since the return of the original case, 26 instances of tuberculous infection and only one case of clinical tuberculosis have been found in their contacts.

Some of the infections and reinfections in these 493 persons, whose contact with a recognized case of active tuberculosis had been interrupted by the isolation order, probably arose from other known and unknown cases in the environment. Tuberculin surveys in Los Angeles have shown an average annual infection attack rate of less than 2 per cent for the entire population, and only about 0.2 per cent of the population are reported to have developed tuberculous disease annually. The higher rates in all groups of the contacts indicate that the environmental exposure, even after isolation of the known sources of infection, was still much greater than that of the community as a whole.

The reduction in infection and disease rates in the contacts after the isolation of the primary cases, in comparison with the corresponding figures during the period between the diagnosis and the isolation, indicates the value of this procedure. This is especially striking in those followed more than a year after the isolation or death of the primary case, or after his release as noninfectious.

All 19 instances of tuberculous disease and more than half of the instances of tuberculous infection, developing in contacts after the issuance of the isolation orders, occurred among the families of only 12 of the isolated patients. The failure to obtain better results from the isolation procedure may be ascribed in part to violation of the orders by these individuals.

SUMMARY

Enforced examination of contacts and compulsory segregation of cases of open tuberculosis have now been in effect in Los Angeles County for more than a decade. More than 2,000 individuals have been made to submit to proper precautions in the control of this disease. Among nearly 500 household contacts of cases of open tuberculosis, 197, or 40 per cent, had already been infected before isolation was invoked, including 59 instances of active disease. During the period of separation from the recognized case, another 80 instances of infection, with 18 more cases of active tuberculosis, developed. After release of the original case as safe, 27 more of the contacts became infected and one developed clinical disease. There remain 189 members of these families who

have not yet been infected, and 415 who have not developed tuberculous disease. Many of these probably owe their escape to the isolation procedure.

CONCLUSION

Despite inherent limitations and practical weaknesses, the isolation of open cases of tuberculosis in Los Angeles County has, over a period of ten years, proved to be legally enforcible, financially feasible, socially acceptable and hygienically valuable. It has improved the medical treatment of the patients isolated, protected many of their contacts from further exposure to infection and disease, and created a popular understanding of the contagiousness of tuberculosis which augurs well for the eventual eradication of the disease.

CONCLUSIONES

A pesar de las limitaciones inherentes al método y sus puntos vulnerables en la práctica, el aislamiento de los casos de tuberculosis abierta en el Condado de Los Angeles ha resultado ser, durante un período de diez anos, cumplible jurídicamente, factible económicamente, aceptable socialmente, y valioso higiénicamente. También ha mejorado el tratamiento médico de los enfermos aislados, protegido a muchos de sus allegados contra la exposición ulterior a la infección y la enfermedad, y creado una comprensión popular de la contagiosidad de la tuberculosis que augura bien para la erradicación de la enfermedad con el tiempo.

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CHEMOTHERAPY OF TUBERCULOSIS[1, 2]

Sulfanilamide by the Intravenous Drip Method

GARY ZUCKER, MAX PINNER AND HAROLD THOMAS HYMAN

Following the successful introduction of massive dose intravenous drip (1) chemotherapy in the treatment of early syphilis (2), a similar study in the treatment of tuberculosis was started at Montefiore Hospital for Chronic Diseases.[3]

Sulfanilamide was chosen as the first drug for investigation. In the guinea pig some degree of inhibition of tuberculosis was reported following the administration of large doses of sulfanilamide by mouth (3, 4, 5, 6, 7). Smaller doses of the drug effected no apparent retardation (8, 9, 10). Clinically, the treatment of pulmonary tuberculosis in man using sulfanilamide by mouth in small doses was found to have neither beneficial nor harmful effects (11, 12).

CLINICAL MATERIAL

Thirteen patients were treated. The duration of their tuberculosis varied from about six months to fifteen years. There were 2 minimal, one moderate and 10 far advanced cases of pulmonary tuberculosis.

Several patients had extrapulmonary foci. Tuberculosis of the larynx was present in 3, of the middle ear in 2, of the gastro-intestinal tract in 2, and of the pharynx, bronchus and genito-urinary tract in one each.

Though an effort was made to obtain patients with exudative lesions and little or no tissue destruction, a few cases of far advanced fibrocavitary tuberculosis, with but little exudative disease, were included. These patients were treated to ascertain the practicability of the method rather than for any possible beneficial effect. For some time preceding the treatment, most of the patients had been observed in the Montefiore Hospital for Chronic Diseases or its Country Sanatorium at Bedford Hills. Therefore the general tendency of the disease and the response to previous therapeutic procedures were well known. A few patients were admitted from outside sources[4] and were treated after a brief observation period on bed-rest.

[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York City.

[2] This project was made possible by the generosity of the late Blanche deJonge, in memory of her husband, Sali W. deJonge.

[3] This study was carried out under the direction of the Research Committee of the deJonge Tuberculosis Project. The personnel of the Committee included Dr. E. M. Bluestone, Chairman, Drs. David Marine, Sol Biloon, Max Pinner and Harold Thomas Hyman, Messrs. Henry L. Moses, Robert D. Steefel, Leo Wallerstein and Howard C. Hirsch.

[4] Department of Hospitals, City of New York: Dr. Willard C. Rappleye, Commissioner; Dr. Allen Kane, Director, Division of Tuberculosis. Department of Health, City of New York: Dr. John L. Rice, Commissioner; Dr. Herbert R. Edwards, Director, Bureau of Tuberculosis.

EVALUATION OF RESULTS

In judging results controls were not used because of the difficulty of constructing a valid control group in clinical tuberculosis. The outcome in each patient was evaluated on the basis of the expectation of the future course of his disease on bed-rest alone. A time limit for therapeutic efficacy was set at about two months. It was felt that a drug specifically effective against tuberculosis would manifest its action after a relatively short period of administration and certainly at most within a period of two months after cessation of treatment. Only unequivocal improvement, such as is not ordinarily seen with bed-rest alone, could be considered as significant.

TECHNIQUE

For the intravenous administration, an 0.8 per cent solution of sulfanilamide[5] was used. At first this was made up in $\frac{1}{6}$ molar sodium lactate solution.[6] Later, normal saline was used as a vehicle.

The intravenous drip was started in one of the forearm veins at about 9:00 a.m. and was continued for ten to eleven hours. This was repeated on each of five successive days.

At first sulfanilamide was given in varying amounts each day to determine the dosage that would maintain a blood level of about 20 mg. per cent. Later, it was found that diurnal blood levels of free sulfanilamide approximating 20 and 30 mg. per cent could be attained by the administration of 0.18 to 0.20 g. of sulfanilamide per kilo on the first day and 0.16 g. to 0.18 g. per kilo on the subsequent days. About 60 per cent of the total daily dose was given during the first four hours.

At the end of the five-day period of intravenous sulfanilamide most of the patients were given small to moderate doses of sulfanilamide by mouth for from one to five days. Because of the debility resulting from the prolonged administration of the drug, the last few patients did not receive sulfanilamide orally.

Nine of the 13 patients received only one course of treatment. Two received two courses and 2 received three courses. The interval between courses varied from three weeks to three and one-half months. Only those patients were retreated who tolerated therapy well and whose disease indicated that some beneficial effect might be expected.

CLINICAL OBSERVATIONS

The patients were watched carefully for all signs of toxic effects of sulfanilamide and for alterations in the clinical course during and after treatment. A daily blood count, platelet count, urine analysis and physical examination were done. X-ray films of the chest, sputum examinations, sedimentation rate and determinations of sputum and body weight were done at frequent intervals.

[5] The sulfanilamide was supplied by E. R. Squibb & Co.

[6] The sodium lactate solution was supplied by Eli Lilly & Co.

Cultures of the sputum for non-acid-fast organisms were made before and after chemotherapy. Other examinations were performed on indication.

Evaluation of change in the patient's condition was made primarily on objective findings, such as serial X-ray films of the chest, sputum, temperature and physical examination. Little importance was attributed to subjective reactions of the patient.

Pharmacology: The total dosage for each course of treatment, including both the intravenous and oral drug varied from 50.2 g. to 86.0 g. Two patients received treatment for only three days during which time 28.3 g. and 37.0 g., respectively, were administered intravenously. The smallest daily dose intravenously was 7.7 g., the largest 15 g.

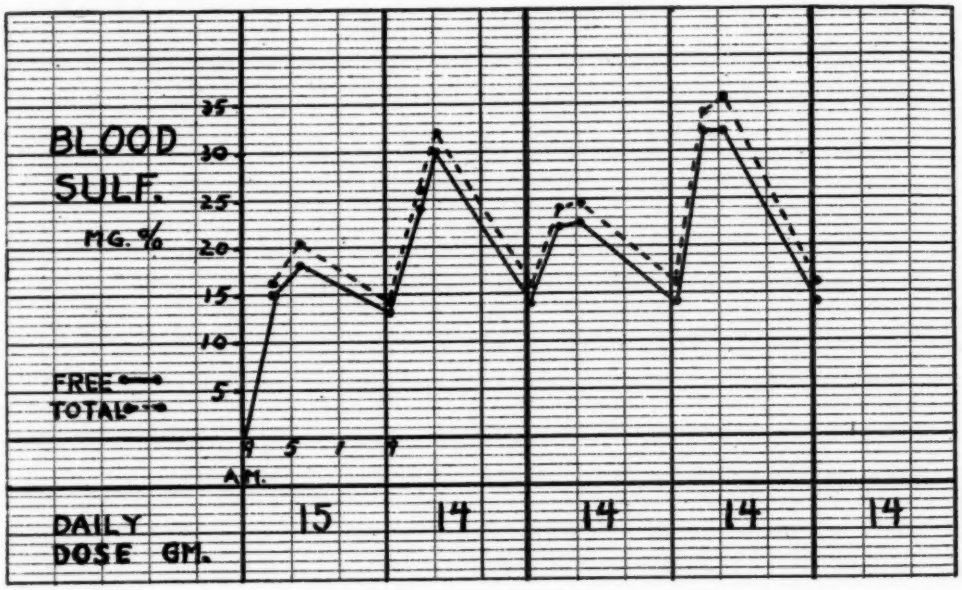

FIG. 1. Blood levels of sulfanilamide during five days of intravenous drip therapy (Patient H. Z., 79 kilo)

Fairly high blood levels were attainable by giving 60 per cent of the total daily dose in the first four hours. The free sulfanilamide level prior to commencing the drip in the morning of the second to the fifth day varied between 8.0 mg. per cent and 20.0 mg. per cent with a mean of approximately 14 mg. per cent. After four hours it usually reached a peak. During the drip administration it was possible to maintain the blood levels between 17.0 mg. per cent and 32.0 mg. per cent (figure 1). There was no exact correlation between the dosage and the blood levels in different patients. Some patients attained higher levels than others on the same dosage.

There was considerable variation in the degree of acetylation, in the same patient at the same hours of different days, and from patient to patient. This ran from a low of 2 per cent to a high of 28 per cent.

Toxicology (Table 1): The usual toxic reactions attributed to sulfanilamide were observed in most of our patients. These symptoms were usually mild to moderate in severity and disappeared promptly after the discontinuation of the drug.

Headache, nausea and anorexia were usually slight to moderate during the intravenous administration of large doses of sulfanilamide. Because of the anorexia all patients had temporary weight loss ranging from two to ten pounds. Vomiting was infrequent. Almost uniformly much smaller doses by mouth caused much more severe gastro-intestinal symptoms. The degree of mental depression varied strikingly from patient to patient. In most cases it was slight and tended to be more marked the higher the blood level of sulfanilamide.

Some degree of fever was observed in all cases. This appeared usually on the first or second day and persisted for from twenty-four to forty-eight hours after

TABLE 1

Incidence of toxic reactions during intravenous drip administration of large doses of sulfanilamide to 13 patients with tuberculosis

Headache	13
Cyanosis	13
Mental depression	13
Dyspnoea	13
Fever	13
Drop in haemoglobin (1.2 to 3.5 g.)	13
Nausea	12
Anorexia	12
Weakness	10
Vomiting	8
Diarrhoea	4
Photophobia	4
Icterus	2
Leucopenia	1
Haematuria	1

the drug had been stopped. The temperature usually did not rise above 102°F. but there were occasional peaks up to 103.6°F. and 104.2°F. in 3 patients.

In 2 patients the intravenous drip was discontinued on the third day because of a severe, shaking chill and temperature elevation to 103.4°F. and 105°F. respectively. In both cases these adverse effects disappeared promptly when the sulfanilamide was stopped. They did not reappear on that and subsequent days in spite of the continuation of the drip with only the vehicle previously used for the sulfanilamide.

One of the latter patients, who had had a microscopical haematuria prior to therapy, developed a painless, gross haematuria. This was associated with albuminuria, cylindruria and one day of oliguria. There was no azotaemia or impairment of concentrating power. These findings subsided completely over a period of several weeks. No crystals of acetylsulfanilamide were found in the freshly voided urine and no calculi were ever demonstrated by cystoscopy or

retrograde and intravenous pyelography. There was, however, some dilatation of the left pelvis and calyces and of the right pelvis. The left ureter was constricted at the junction with the pelvis. These changes undoubtedly antedated sulfanilamide therapy. No tubercle bacilli could be isolated from the urine or prostatic secretions by smear, culture or guinea pig inoculation. The exact cause of the haematuria could not be determined, but it was felt that the sulfanilamide may have contributed to its production. To our knowledge no evidence of renal irritation caused by sulfanilamide has ever been recorded for man.

In 2 patients a mild icterus of the sclerae appeared on the eighth day of sulfanilamide administration. Serum bilirubin levels were 1.4 mg. per cent and 2.0 mg. per cent, respectively. In neither case was there any bilirubinuria or marked haemolysis. The icterus was most likely on the basis of mild haemolysis and suppression of liver function.

In one patient there was a drop in the differential count from 77 per cent to 45 per cent polymorphonuclears without any decrease in the total leucocyte

TABLE 2

Incidence of certain clinical and laboratory changes observed in 13 tuberculous patients receiving sulfanilamide by intravenous drip

Fever	13
Leucocytosis	11
Increased sedimentation rate	10
Chills or chilliness	10
Night sweats	8
Increased cough	6
Increased sputum	7
Looser sputum	11
Increased râles (excluding 5 cases with many râles at start)	6

count. The differential count returned to normal promptly after the cessation of the drug.

All patients developed slight to moderate dyspnoea. Simultaneously, in 6 patients tested, there was a drop of the carbon dioxide combining power to from 32 to 49 vol. per cent. This appeared in spite of the intravenous administration of 1,200 to 1,440 cc. of one-sixth molar sodium r. lactate daily for five days.

Except for 2 patients who had high fever and shaking chills on the third day of treatment, there were no other instances where the intravenous drip had to be discontinued because of toxic reactions.

Special changes occurring during therapy: In most patients there was observed a group of clinical and laboratory changes which may be of special significance. These included fever, elevation of the erythrocyte sedimentation rate, increased leucocytosis, increased cough and sputum, looser sputum, increased pulmonary râles over the diseased areas, chilliness or chills and night sweats (table 2). With the exception of the elevated sedimentation rate, all of these subsided soon after discontinuation of the drug. The restitution of the sedimentation rate to its

pretreatment level usually required two to four weeks. This combination of findings might be the result of changes in the tuberculous tissue produced by sulfanilamide. Again, it might be a reaction to the drug itself though no such reaction has been as yet recorded in the literature.

CLINICAL RESULTS

Of the 13 patients treated, 5 showed no clinical change. Of the latter, 2 were treated for only three days.

Three patients improved slightly.

Four patients showed continued progression of the disease.

One patient with disseminated haematogenous tuberculosis, whose prognosis prior to chemotherapy had been considered as hopeless, died.

Complete or permanent sputum conversion did not occur in any of the patients. In one patient with minimal tuberculosis, the sputum became negative immediately following the first course of treatment. Two gastric contents were negative on culture. However, four months later while on a semi-ambulant regimen, one sputum was found to be positive.

In no case was any beneficial or adverse effect on the pulmonary tuberculosis noted that could be attributed to chemotherapy.

Effective chemotherapy in pulmonary tuberculosis would probably be most successful in patients in good general health and with early, exudative lesions. Poor resistance, rapidly progressive, far advanced disease, old productive lesions and extensive cavitation would tend to hamper the action of any specific drug. Therefore, in our opinion, the final evaluation of the efficacy of any drug should be made on patients that are most suitable for chemotherapy from the standpoint of being in good general health, and having early, exudative disease with little or no tissue destruction. If sufficient amounts of a drug were to be given to such patients and rapid improvement were not obtained then it could be said that the drug lacked any specific effect. The following case report illustrates these criteria.

H. Z., a twenty-one year old white laborer, was admitted on April 4, 1941. A pulmonary lesion in the right apex was found on routine preëmployment X-ray film one month prior to admission. Patient had been perfectly well except for slight fatigue and weight loss during the preceding six months. Two concentrated sputa were negative for tubercle bacilli at the Board of Health Clinic. Patient was on bed-rest at home for one month prior to admission to Montefiore Hospital. At this time the only symptoms were slight weakness and cough and occasional pain over the right apex. Examination revealed a well developed and well nourished male who did not appear ill. A few post-tussive râles were heard in the right supraclavicular area. X-ray film of the chest taken on April 5, 1941 revealed a soft, exudative infiltration involving the upper half of the right upper lobe. No cavity was seen (figure 2). Comparison of this film with one taken on March 20, 1941 showed no change in the pulmonary lesion. Concentrated sputa were alternately positive and negative. Sputum was 10 to 20 g. daily; red cell count, 5,140,000; haemoglobin, 15 g.; white cell count, 13,000; neutrophiles, 66 per cent; staff cells, 2 per cent; basophiles, 1 per cent; lymphocytes, 24 per cent; monocytes, 7

per cent; sedimentation rate 10 mm.; urine was normal; temperature, pulse and respirations were normal. Patient was put on bed-rest and was given chemotherapy from April 8, 1941 to April 15, 1941, employing 0.8 per cent sulfanilamide in normal saline solution; 71 g. of sulfanilamide were administered during the first five days by intravenous drip, followed by 15 g. in the next three days by mouth. Toxic effects of sulfanilamide were slight and included headache, nausea, anorexia, cyanosis, dizziness, dyspnoea, photophobia, icterus and fever. Serial X-ray films showed no significant change in the minimal pulmonary infiltrate. Sputum remained positive on concentration. Two weeks later patient was given another course of sulfanilamide therapy. From April 29, 1941 to May 3, 1941 he received a total of 71 g. of sulfanilamide intravenously (figure 1). No sulfanilamide was given by mouth. Serial X-ray films during a period of ten weeks after the start of sulfanilamide therapy showed only slight decrease in the size of the

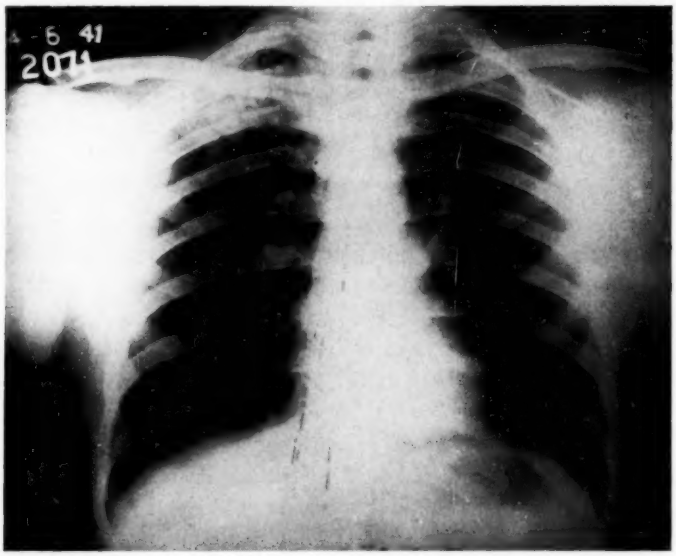

FIG. 2. (H. Z.) Chest film taken before treatment on April 5, 1941

pulmonary lesion. Sputum remained alternately positive and negative on concentration. There was no change in the amount of sputum. Temperature, pulse, respiratory rate, leucocyte count and sedimentation rate remained normal. Weight was stationary. General condition was excellent. The amount of improvement in this patient was not more than could be expected on bed-rest alone.

Effects on mucosal complications: Special mention should be made of the behavior of mucosal lesions in 5 of the patients. Three patients with active tuberculous laryngitis showed a temporary improvement in the amount of oedema and infiltration during and for one to two weeks after treatment. In all likelihood, this resulted from the effect of the drug upon a superimposed secondary infection. Cultures of the sputa before chemotherapy in all cases showed the usual organisms: *Streptococcus non-haemolyticus*, *Streptococcus viridans*, staphylococci, diphtheroids and *Micrococcus catarrhalis*. There was no significant change

in the flora after chemotherapy. In no case was *Streptococcus haemolyticus* isolated.

In one patient there was severe dysphagia prior to treatment preventing the patient from eating. On the third day of intravenous sulfanilamide administration the dysphagia and some of the hoarseness disappeared dramatically. This was associated with a striking subsidence of the oedema of the arytenoids and ventricular bands. The patient felt so well that he left the hospital against advice. Subsequently, the same symptoms and laryngeal involvement returned and were followed by extension of the mucosal lesions into the mouth and pharynx. This patient died with marked toxaemic symptoms nine and one-half weeks after chemotherapy had been started.

Two other patients had mucosal lesions. One, with a haematogenous lesion of both upper lobes, developed a superficial ulcer about three-fourths inch in diameter on the posterior pharyngeal wall. The borders of the ulcer were sharp and the base contained many small granulations. The ulcer first appeared four weeks after the first course of sulfanilamide. The ulcer healed completely over a period of three months during which time the patient received two more courses of sulfanilamide by intravenous drip.

The second patient had been observed on bed-rest for two months prior to receiving chemotherapy. During that time there were noted sibilant and sonorous râles over the right base and a fairly rapid development of a localized area of homogeneous density in the right lower lobe. An endobronchial lesion was suspected but unfortunately the patient could not be bronchoscoped before treatment with sulfanilamide was started. During the first course of treatment the musical râles disappeared almost entirely and X-ray films showed a marked reduction in size of the area of density in the right lower lobe. Bronchoscopy performed on the ninth day of treatment disclosed a caseated lesion of the anterolateral division of the right lower lobe bronchus with almost complete occlusion of the lumen. Three weeks later the lesion was seen to be smaller and the lumen wider. The patient was treated again six weeks after the first course. At this time only an occasional sibilant râle was heard at the right base. X-ray films showed further decrease in the size of the dense area. Bronchoscopy at this time, seven weeks following the first one, revealed a further decrease in the size of the endobronchial lesion, an increase in the size of the lumen and less secretion from the bronchus. The patient received a third course of treatment with sulfanilamide five weeks after the second course. By this time the sibilant râles had completely disappeared. Bronchoscopy performed six weeks later, or three and one-half months after the first course of treatment, demonstrated that the endobronchial lesion had completely healed, leaving behind a slight stenosis of the bronchus. At no time was any local treatment applied to the lesion. In the opinion of the bronchoscopist the rate of healing without local cautery was more rapid than usual. It is of interest to note that, simultaneously with the healing of this tuberculous lesion, there was slight progression of the infiltrations present in the opposite lung.

SUMMARY

1. Thirteen patients with pulmonary tuberculosis were treated with one to three courses of large doses of sulfanilamide given by the intravenous drip method. High blood concentrations of free sulfanilamide were maintained.

2. Sulfanilamide given by the intravenous drip method produced the usual toxic reactions. Nausea and vomiting were less severe while fever, chilliness and dyspnoea were more frequent. One patient developed a gross haematuria possibly related to the sulfanilamide. Two patients had chills and fever on the third day of intravenous sulfanilamide treatment, necessitating cessation of treatment.

3. While sulfanilamide was being given by intravenous drip, fever, increase of cough, sputum and râles, elevated sedimentation rate and leucocytosis associated with occasional chilliness or chills and night sweats were observed in most patients.

4. Of the 13 patients, 11 had at least five days of intravenous sulfanilamide therapy. Of these, 7 had one course of treatment and no striking, specific improvement was noted in any.

5. Two patients with minimal pulmonary tuberculosis received two courses of treatment and showed slight resorption over a period of two and one-half months and four months, respectively. In one of these patients there was sputum conversion with two negative gastric cultures after the first course of treatment, but four months later the sputum was positive again. In neither case was the improvement better than could be expected on bed-rest alone.

6. Two patients received three courses of sulfanilamide intravenously. One showed slight progression in the lesions of the left lung over a period of three and one-half months, but simultaneously there was complete healing of an endobronchial tuberculous lesion. The other patient demonstrated some resorption of infiltrates in both apices after six months and complete healing of a tuberculous pharyngeal ulcer in three months.

7. Permanent or complete sputum conversion was not obtained in any case.

8. In 3 instances there was temporary improvement of the oedema and filtration of the tuberculous laryngitis during and for one to two weeks following sulfanilamide therapy. Ultimately there was steady progression of these lesions. The improvement was probably due to the clearing of a secondary pyogenic infection.

9. Two other mucosal lesions healed during the period of treatment: a pharyngeal ulcer in three months and a caseous endobronchial lesion in three and one-half months.

SUMARIO

1. A 13 tuberculosos pulmonares se les trató con una a tres series de dosis masivas de sulfanilamida, administradas con la técnica del goteo intravenoso. Se mantuvieron en la sangre concentraciones elevadas de sulfanilamida libre.

2. La sulfanilamida administrada con la técnica del goteo intravenoso produjos las habituales reacciones tóxicas, siendo las náuseas y los vómitos los menos intensos y más frecuentes la fiebre, los escalofríos y la disnea. Un enfermo manifestó una hematuria macroscópica posiblemente relacionada con la sulfanilamida, y dos manifestaron escalofríos y fiebre al tercer día de recibir sulfanilamida por vía venosa, obligando a suspender el tratamiento.

3. Mientras se administraba la sulfanilamida con el goteo endovenoso, en la mayor parte de los enfermos se observaron fiebre, aumento de la tos, esputo y estertores, elevación del coeficiente de sedimentación y de la leucocitosis, asociados a veces con enfriamientos o escalofríos y sudores nocturnos.

4. De los 13 enfermos, 11 recibieron por lo menos durante cinco días la sulfanilamidoterapia intravenosa. De ellos, 7 recibieron una serie terapéutica, sin observarse en ninguno notable mejoría específica.

5. Dos enfermos que padecían de tuberculosis pulmonar mínima recibieron dos series terapéuticas y revelaron ligera reabsorción durante un período de dos y medio y cuatro meses respectivamente. En uno de estos enfermos se observó conversión del esputo y dos cultivos gástricos resultaron negativos después de la primera serie, pero a los cuatro meses el esputo era positivo de nuevo. Ni en uno ni en otro caso fué la mejoría superior a la que podría esperarse con el descanso en cama exclusivo.

6. Dos enfermos recibieron tres series intravenosas de sulfanilamida. Uno reveló ligera agravación de las lesiones del pulmón izquierdo durante un período de tres meses y medio, pero simultáneamente cicatrización completa de una lesión tuberculosa endobronquial. El otro enfermo reveló alguna reabsorción de los infiltrados en ambos vértices al cabo de seis meses, y completa cicatrización de una úlcera faríngea tuberculosa en tres meses.

7. En ningún caso se obtuvo conversión permanente o completa del esputo.

8. En tres casos hubo mejoría temporal del edema e infiltración de la laringitis tuberculosa durante la sulfanilamidoterapia y por una a dos semanas después, pero por fin se manifestó agravación constante de esas lesiones, debiéndose probablemente la mejoría a la extinción de una piogenia secundaria.

9. Otras dos lesiones de las mucosas curaron durante el período de tratamiento: una úlcera faríngea en tres meses, y una lesión endobronquial en tres y medio meses.

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PROMIN IN EXPERIMENTAL TUBERCULOSIS[1]

Sodium P,P′-Diaminodiphenylsulfone-N,N′-Didextrose Sulfonate

WILLIAM H. FELDMAN, H. CORWIN HINSHAW AND HAROLD E. MOSES

The success achieved in recent years by the use of certain of the newer chemotherapeutic agents in combating a variety of specific infectious diseases has provided reasons for believing that eventually a compound or compounds will be found that will be useful clinically in the treatment of tuberculosis. Interest in the problem was revived by the report of Rich and Follis (1) who in 1938 reported that sulfanilamide had an inhibitory effect on the development of experimental tuberculosis in guinea pigs. Since the report of Rich and Follis several additional papers have appeared and, although valuable information on the resistance and vulnerability of the tubercle bacillus has been revealed, the long awaited and fervently hoped for chemical agent that will combat successfully tuberculous infections in human beings remains to be demonstrated. However, as the search continues and newer compounds are made available, what were considered previously perhaps as futile efforts now assume a new importance and provide a measure of confidence for believing that effective chemotherapeutic agents will be found eventually.

Previously (2, 3) we have reported our preliminary observations on a newer compound known chemically as sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate. This compound was designated by the manufacturer as "promin." An official designation for the drug has not been agreed upon as yet; therefore for the sake of brevity the term promin will be used throughout this report. The promin utilized in the subsequent studies was supplied through the courtesy of Dr. E. A. Sharp, Parke, Davis and Company, Detroit, Michigan.

CHEMICAL STRUCTURE AND PROPERTIES OF PROMIN

The structural formula assigned to promin is illustrated in figure 1. It will be seen that this compound is related to 4,4′-diaminodiphenylsulfone. The early work on the latter compound has been summarized by Long and Bliss (4). The parent substance (4,4′-diaminodiphenylsulfone) is a highly effective chemotherapeutic agent, but its toxicity has limited its application. The addition of the glucose radicals and the sodium sulfonate groupings apparently has the effect of increasing the solubility of the substance and decreasing its toxicity and perhaps its therapeutic efficacy. However, promin has demonstrated its ability to combat successfully infections caused by the haemolytic

[1] From The Mayo Foundation, Rochester, Minnesota.

streptococcus, the pneumococcus, the gonococcus and probably other organisms (5, 6, 7).

Promin in its solid form varies from white to light yellow and is slightly hygroscopic. It is highly soluble in water and 40 per cent solutions are stable indefinitely and may be sterilized by heat. The drug is slightly bitter but may be mixed with the food of experimental animals without apparently impairing their appetite or producing any other recognizable gastro-intestinal disturbance. Guinea pigs tolerate 1 per cent promin in their food quite satisfactorily. They will consume from 30 to 40 g. of the dry food mixture which is made available during each twenty-four hours. This results in a consumption of promin of from 300 to 400 mg. per twenty-four hours. If the concentration of promin be increased to 2 per cent in the food, deleterious effects are noted, including anorexia which interferes with the quantity of food taken and the amount of drug consumed.

Our experience with the parenteral administration of promin to guinea pigs has not been satisfactory. If a large number of animals are to be treated over

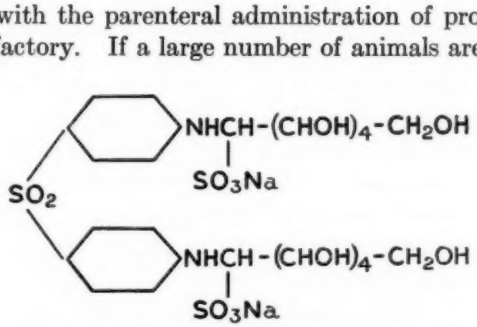


FIG. 1. Structural formula of promin

a prolonged period, the frequent injection of any substance becomes a laborious and time consuming procedure. Consequently the convenience of oral administration of a drug that can be combined with the feed is obvious. A few preliminary observations were made in which promin was given subcutaneously to apparently normal guinea pigs. The puncture wounds produced by the hypodermic needle did not seem to heal and continued to ooze blood when manipulated many days later. Whether promin administered parenterally would have an effect comparable to that of promin administered orally in experimental tuberculosis of guinea pigs is not known.

FIRST EXPERIMENT

When the first of these reports was prepared for publication, a detailed study of the material had not been completed. Consequently it is appropriate to give a résumé of our first study before describing in detail the second.

Methods: In the first experiment 50 male guinea pigs were divided into two groups. One group of 30 animals received promin while the remaining 20 animals were considered as controls. Promin to the amount of 1 per cent was added to the feed of the animals that received the drug as a prophylactic or therapeutic measure, the administration of the drug being started two days before infection with tubercle bacilli was introduced.

The diet consisted of so-called rabbit chow to which was added corn syrup to the amount of 2.5 per cent. The syrup was for the purpose of making the feed containing promin more palatable. The diet mentioned was supplemented twice weekly with leafy vegetables and stock beets.[2] Each guinea pig consumed between 30 and 40 g. of feed each twenty-four hours and, since the feed was available to the animals most of the time, the intake of the drug was more or less continuous. Most of the animals became accustomed to the feed containing the drug within a few days. All the guinea pigs then were inoculated subcutaneously with 0.000,5 mg. of human tubercle bacilli strain H37RV.[3] A subculture of this strain was kindly supplied by Dr. H. J. Vorwald, Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, New York. The animals in the treated group continued to receive promin in their daily diet for eighty-four days at which time all the animals in the control group had died. On the eighty-fourth day, 24 of the animals that had received promin were living. Promin was removed from the diet of 12 of the survivors, while the drug was continued in the diet of the remaining 12 guinea pigs. The experiment was continued for a period of eighty-two days more when the 13 surviving animals were killed. Of the 13 guinea pigs living when the experiment was terminated, 5 had received promin for the entire period (166 days) and the other 8 animals did not receive promin during the last eighty-two days of life. The purpose of this procedure was to determine if latent tuberculosis would become reactivated when treatment was discontinued.

The concentration of promin in the blood was determined on one occasion during the first phase of the period of observation. It varied from 2.3 to 4.3 mg. per 100 cc. of blood. The tests to determine the concentration of promin in the blood in this and in the subsequent experiment were conducted by Dr. A. E. Osterberg and his associates in the Section on Clinical Biochemistry.

Results: In appraising the effects of any chemotherapeutic agent on an experimentally induced tuberculous infection, two factors are of importance: the survival time and the extent and character of the disease process. The fact that, at the time when all the control animals were dead, 83 per cent of the animals that were receiving the drug were still living seems significant. This should not be overemphasized, however, since in this first experiment nutritional disturbances which contributed to the mortality developed in both treated and control groups. The nutritional difficulties may have interfered with adequate intake of promin by treated animals and also may have produced death of some control animals before maximal lesions of tuberculosis developed.

A comparison of the amount and character of tuberculosis in the two groups also revealed some important differences. For convenience the incidence of tuberculous involvement in the spleen, liver and lungs of the treated and untreated groups of guinea pigs is summarized in table 1. With one exception (mentioned in footnote 4) the degree of tuberculous involvement in the animals

[2] The necessity of supplementing the basic diet with fresh vegetables was not recognized when the first experiment was started. As mentioned later, it was found that the rabbit chow was inadequate for the nutritional requirements of guinea pigs unless the proper supplements were added.

[3] H37RV is one of two variants dissociated from strain H37. The biological characteristics of the RV variant have been studied comprehensively and reported on by Oatway and Steenken (8) who considered the organism to be of high virulence.

that received promin was notably less than in the controls. Fewer situations were affected and the lesions were fewer and of smaller size than in the animals that were untreated. Furthermore in the spleen, liver and lungs of approximately 50 per cent of the animals that had received promin there were no cellular reactions that could be considered tuberculous when observed either grossly or microscopically. In the control group, although the animals were all dead in eighty-two days, all had lesions of progressive tuberculosis in one or all of these organs of predilection.

Not only were fewer of the visceral organs of predilection affected in the animals that received promin than in the controls, but also there was less demonstrable disease at the site of the inoculation and in the contiguous lymph nodes of the treated animals than in the animals that were not treated.

Although the results indicated that in many of the animals promin either had prevented the establishment of lesions or had caused their eventual disap-

TABLE 1

Summary of comparative amounts of tuberculosis in the treated and the untreated groups of guinea pigs (experiment 1)

ORGAN	GROUP 1, 30 ANIMALS THAT RECEIVED PROMIN.* ANIMALS LIVED FROM 60 TO 164 DAYS	GROUP 2, 20 ANIMALS NOT TREATED. ANIMALS LIVED FROM 46 TO 82 DAYS
Spleen	29 examined. Tuberculosis in 12, or 41 per cent	19 examined.† Tuberculosis in 19, or 100 per cent
Liver	28 examined.† Tuberculosis in 5, or 18 per cent	20 examined. Tuberculosis in 9, or 45 per cent
Lungs	28 examined.† Tuberculosis in 5, or 18 per cent	19 examined.† Tuberculosis in 5, or 26 per cent

* One animal died prematurely.

† Section of one not available for examination.

pearance, another effect of the drug which is perhaps of more importance was that which it exerted on the cellular elements of the lesions. In the vast majority of the animals in the treated group that had lesions, the histopathological characteristics of the disease process apparently were modified favorably.[4] This was especially true of the lesions in the parenchymal tissues. The lesions were usually small and discrete and the epithelioid phase of the reactive process predominated. Necrosis was infrequent and a tendency of the process toward fibrosis was observed frequently. These features of the morbid process were in marked contrast to those that characterized the disease in the control group of animals. In the latter the disease was extensive, destructive and progressive.

[4] Exception in the case of one guinea pig should be noted. The animal lived one hundred and thirty-three days after being infected and had received promin during the entire period. The amount of tuberculosis present in this animal was most impressive. In addition to massive involvement of the spleen and a striking tuberculous pneumonia, there was evidence of extensive haematogenous tuberculosis. The mononuclear cells of the lungs and spleen contained enormous numbers of acid-fast bacillary forms. The animal had become in fact a living culture medium for tubercle bacilli.

An effort was made to detect the presence of tubercle bacilli in spleens which appeared grossly to have no lesions. Each of 17 spleens of treated animals was divided and a portion suspended for inoculation into two additional guinea pigs. The results of this portion of the study are shown in table 2. Of the 17 spleens, 9 contained viable tubercle bacilli and 8 did not. Viable tubercle bacilli were observed in all but one of the 5 spleens in which lesions of tuberculosis were present microscopically and positive results were obtained from 5 spleens in which lesions of the disease were not found. Lesions of tuberculosis were found in the spleen of only one of the 5 guinea pigs that had received

TABLE 2

Summary of results of animal inoculations to determine presence of viable tubercle bacilli in spleens of previously infected guinea pigs that had received promin for variable periods (experiment 1)

ANIMAL	GUINEA PIGS THAT RECEIVED PROMIN			RESULTS OF INOCULATION OF GUINEA PIGS
	Received promin in days	Days before death	Spleen*	
1	84	166 killed	−	Negative
2	84	166 killed	−	Tuberculosis
3	84	166 killed	+	Tuberculosis
4	84	166 killed	+	Tuberculosis
5	84	166 killed	+	Tuberculosis
6	84	166 killed	−	Negative
7	84	166 killed	−	Tuberculosis
8	84	166 killed	−	Negative
9	84	128 died	−	Negative
10	111	111 died	−	Negative
11	117	117 died	−	Tuberculosis
12	133	133 died	+	Tuberculosis
13	166	166 killed	+	Negative
14	166	166 killed	−	Negative
15	166	166 killed	−	Negative
16	166	166 killed	−	Tuberculosis
17	166	166 killed	−	Tuberculosis

* Presence or absence of lesions of tuberculosis determined microscopically is indicated by a plus or minus sign.

promin for the entire period of observation (166 days). Three of the 5 spleens in which lesions were found were from animals that had received the drug for eighty-four days only. These observations make it evident that tubercle bacilli may persist in the apparently nontuberculous splenic tissues of animals that have received promin for as long as one hundred sixty-four days after infection and be capable of inducing lesions of tuberculosis in untreated guinea pigs although they presumably were unable to do so in animals receiving promin. That many of the spleens were free of virulent tubercle bacilli, presumably as a consequence of the promin, likewise was established. Tubercle bacilli may be latent in tissues of guinea pigs long after treatment is discontinued. Since

subinoculation proved the virulence of the dormant organisms, this latency suggests the possibility that immunity developed in these animals.

The information obtained in this experiment provided sufficient reasons for concluding that promin under the conditions imposed had a definite chemotherapeutic effect on a tuberculous infection induced in a highly susceptible animal with a strain of human tubercle bacilli of known virulence. The longer survival time of the treated animals, the lesser amount of actual disease present and the nonprogressive nature of the lesions in the animals that received promin constitute reasonably convincing evidence in support of the foregoing conclusion.

SECOND EXPERIMENT

Since it had been established in our first experiment that the expected course of experimental tuberculosis in the guinea pig could be modified when the administration of promin was started before the infection was introduced, it became desirable to extend our observations. The objectives of our second experiment were twofold: (*1*) to confirm, if possible, the results of our first experiment and (*2*) to determine what effect, if any, promin might have on a tuberculous infection introduced at the same time as or at varying periods before treatment with promin was begun.

Methods: Eighty male guinea pigs of comparable size and apparent good health were selected. The average weight of the animals was approximately 500 g. The animals were divided into eight groups on the basis of the relation of the time of inoculation with tubercle bacilli to the time of commencement of administration of promin. This relation for the respective groups was as follows: Group 1 consisted of 12 animals, infected but not treated; these were considered as controls. Group 2 consisted of 8 animals in which the administration of promin was begun on the day of infection. Group 3 consisted of 8 animals whose treatment with promin started three days after inoculation. Group 4 consisted of 8 animals whose treatment with promin started one week after infection. Group 5 consisted of 8 animals whose treatment with promin started two weeks after infection. Group 6 consisted of 8 animals whose treatment with promin started four weeks after inoculation. Group 7 consisted of 8 animals whose treatment with promin started six weeks after inoculation. Group 8 consisted of 20 animals that received promin for two days prior to inoculation with tubercle bacilli. In all groups the administration of promin was continued daily for the duration of the experiment. The last mentioned group was included to determine whether or not the results obtained in the first experiment could be confirmed. The animals were caged in pairs.

The diet was the same as described in experiment 1 and the amount of promin incorporated in the feed for the treated animals was 1 per cent.

Each of the animals was inoculated subcutaneously in the tissues overlying the sternal region with 0.000,5 mg. of a fifteen day old culture of H37RV. The bacteria were grown on the synthetic medium of Proskauer and Beck (9), for a period of fifteen days, ground with sterile ox bile and suspended in physiological solution of sodium chloride.

When animals died or were killed, a careful necropsy was done and tissues of importance to subsequent studies were preserved in 10 per cent neutral solution of formalin. The necropsy included the following: site of inoculation, axillary and cervical regions;

the liver, spleen, lungs and contiguous lymph nodes; the mesentery, kidneys and bladder. From each of these tissues material was preserved for the making of histological preparations. In most instances the spleen was preserved *in toto* in order to determine the weight of this organ and so that photographs could be made.

All tissues obtained at necropsy, whether they contained gross lesions of tuberculosis or not, were prepared for microscopical study; thus material became available for a comparative study of the histopathology of the tuberculous changes in the various groups of animals.

Tuberculin tests: Tuberculin tests were made during the course of the experiment. These were made seventy-four, one hundred twenty-nine and one hundred seventy-two days after the animals had been inoculated with tubercle bacilli. The product used was Gilliland's Old Tuberculin, diluted 1:100; 0.03 to 0.04 cc. was injected intracutaneously. The results were recorded forty-eight hours after the tuberculin had been injected.[5]

With the exception of one animal in which the reaction was recorded as doubtful and which died after the first test, all guinea pigs tested showed sensitivity to tuberculin. Six animals had died before the first test, 14 before the second test and 21 before the third test. While we attach no significance to the severity of the reaction to tuberculin as indicative of the severity of the disease in the reacting animal, it was of interest to note that with one exception the reactions of animals in the control group to the first test were classified as plus 2 to plus 4. In the exception the reaction was recorded as plus 1. Generally speaking, the reactions of the animals that were receiving promin were less severe than those of the untreated animals. The data regarding 8 of the treated animals in which the reaction to the last test was recorded as doubtful are of some interest and are summarized in table 3.

In only one instance (animal 7) was a reaction of moderate severity recorded. In all others, except as previously noted, the reaction to the initial test, while definitely positive, was of minimal severity. That infection had become established in these animals is indicated by the fact that one or more definitely positive reactions to tuberculin occurred. That no lesions of tuberculosis were found in 5 of the animals and that the lesions in 2 were uncertain or minimal and nonprogressive suggest that, had subsequent tuberculin tests been done, the sensitivity to tuberculin in these animals might have disappeared entirely.

It may be significant that doubtful reactions to tuberculin occurred only in animals that had been receiving promin. No doubtful reactions were observed in the control group.

Concentration of promin in the blood: In the use of any chemotherapeutic agent, to determine its effects on a wide-spread and systemic infection, such as experimental tuberculosis in guinea pigs, it is of importance to ascertain what the concentration of the drug is in the circulating blood. Since the method required about 3 cc. of blood for the determination of the concentration of promin in the blood, we found that the most satis-

[5] The scheme used to record the reaction was that proposed by Aronson (10) in which positive reactions are classified as one, two, three or four-plus.

factory method of collecting the specimen from the live animal was by cardiac puncture. However, when a large number of specimens is to be secured, the procedure is time consuming and is associated with some hazard to the life of the animals. For these reasons we deferred this part of the study until the experiment was terminated. The animals were rendered unconscious with chloroform and the heart was exposed so that the required amount of blood could be obtained while the heart still was pulsating. Coagulation was prevented by a small amount of powdered potassium oxalate and the specimens were kept in the refrigerator until the tests for promin were made. As in the first experiment the concentration of promin in the blood was determined by Dr. A. E. Osterberg and his associates of the Section on Clinical Biochemistry.

TABLE 3

Summary of tests to determine sensitivity to tuberculin in treated animals in which the reaction to the last test was recorded as doubtful (experiment 2)

Animal	Beginning of therapy in relation to infection	Tuberculin tests in days after infection			Days before death	Lesion of tuberculosis
		74	129	172		
1	2 days before	+1	±	±	192 killed	One cirrhotic lesion, axillary lymph node
2	2 days before	+1	Neg.	±	192 killed	None found
3	2 days before	+1	±	±	192 killed	None found
4	Same day	+1	±	Not done	157 died	None found
5	3 days after	+1	+1	±	192 killed	Minimal disease in one lung
6	3 days after	+1	+1	±	192 killed	Uncertain in one lung
7	1 week after	+2	±	±	192 killed	None found
8	1 week after	±	Not done	Not done	120 died	None found

Explanation of symbols:

+1 indicates a positive reaction characterized by some erythema and definite oedema more than 5 mm. and not exceeding 10 mm. in diameter.

+2 indicates a positive reaction characterized by erythema and oedema measuring from 10 to 20 mm. in diameter.

± indicates a doubtful reaction.

Of the 57 specimens examined the highest concentration of promin was 8.6 and the lowest 2.5 mg. per 100 cc. of blood. The average concentration for the 57 specimens was 4.3 mg. Approximately half of the guinea pigs from which the specimens of blood were obtained were killed just before receiving their feed containing the twenty-four hour dose of promin and the others were killed about six hours after receiving the feed containing the drug. No significant differences were observed in the concentration of promin in the two groups of animals. Apparently, when the drug is given by mouth the absorption is slow and rather continuous over a period of many hours.

Toxic effect of promin: Although promin seemed to be tolerated relatively well by the guinea pigs in this experiment, it was noted that promin administered to guinea pigs over a prolonged period had some toxic effects. Whether unphysiological effects of the drug were responsible for the death of any of the 11 treated animals that died during the course of the experiment is problematic.

All animals that received promin remained in apparently excellent physical condition and the vast majority of them had acquired considerable additional weight during the six months of observation. In fact, at the termination of the experiment the weight of many had doubled since the beginning of the experiment. The animals were alert and moved and responded to extraneous stimuli in a manner comparable to that of normal healthy guinea pigs. At necropsy all were excessively fat. Evidence of morphological changes in the urinary tract that could be attributed to the drug was not revealed, although both kidneys and the bladder of each animal that had received the drug were examined microscopically.

However, regardless of the fact that the general physical condition of the guinea pigs remained satisfactory, changes indicative of toxic manifestations were noted in the blood and in the spleen. The blood and the spleen became quite dark and most of the spleens were slightly to markedly swollen. By spectroscopic methods Dr. Charles Sheard of the Division of Physics and Biophysical Research demonstrated sulfhaemoglobin in a large number of specimens of blood examined. In a few instances blood pigment of undetermined character was noted. All the spleens were stained appropriately and an abnormal amount of iron was found to be present in most of them. Other haematological studies, as yet incomplete, indicate that in guinea pigs promin may induce a haemolytic type of anaemia of slight to moderate severity but adequate regeneration was indicated by a corresponding reticulocytosis.

Survival time: One of the most striking facts in this experiment was the marked difference in the survival times of the groups of animals that received promin in comparison with the group that was untreated. The comparative survival times of the animals in the respective groups are shown in table 4. It seems significant that when the last of the untreated animals died, one hundred eighty-nine days after inoculation with tubercle bacilli, 57, or 84 per cent, of the animals that were receiving promin were still living. Only 11, or 16 per cent, of the treated animals had died during the period of observation and none of these had sufficient tuberculosis to account for death. This latter figure represents what reasonably might be considered an average or a normal mortality rate for guinea pigs, even though they were not part of an experimental study. The natural deaths occurred among each of the groups of treated animals except the group in which treatment with promin was started three days after inoculation with tubercle bacilli. In only one group did as many as 3 animals die.

If in work of this character differences in the survival time between the treated and untreated animals are of importance in appraising the effects of a chemotherapeutic agent on an experimental tuberculous infection, the results in this instance appear significant. That the life of 84 per cent of the treated animals was extended beyond the survival time of the untreated controls indicates that a factor or factors were operative in the treated animals that were not apparent in the untreated ones. If it can be assumed that all animals received a comparable infective dose of tubercle bacilli and, allowing for ob-

scure inherent differences in susceptibility of the guinea pigs to the infection, the conclusion cannot be avoided that the animals that received promin tolerated the infection far better than those that did not receive promin. As will be brought out later, this does not imply that tuberculosis did not develop in the animals that received promin—in many it did—but compared to the controls the disease in the animals that received promin was less malignant and was unable to exert a lethal effect in the time required for the disease to do so in animals that had not received promin.

Amounts of tuberculosis in the treated and untreated groups of animals: Before comparing the results observed in the different groups of animals it will be appropriate to present briefly evidence that we actually were concerned with a

TABLE 4

Comparative survival times of guinea pigs in the different groups (experiment 2)

TREATMENT IN RELATION TO INFECTION	GUINEA PIGS	DEATH, MONTHS AFTER INFECTION							KILLED AT 192 DAYS
		1	2	3	4	5	6	7	
Not treated	12	1		3	2	3	2	1 (189 days)	
Two days before	20	1				1			18
Same day	8						1		7
Three days after	8								8
One week after	8				2				6
Two weeks after	8			1			1		6
Four weeks after	8					1	2		5
Six weeks after	8			1					7
Total treated	68								
Total treated that died	11								
Total treated that lived	57 (84 per cent)								

tuberculous infection not only in the control group but also in the groups that received promin. First, the infecting bacterium used represents a well known strain of tubercle bacilli which, when grown according to the procedure described previously and injected subcutaneously in 0.000,5 mg. doses into guinea pigs, in our experience has set up in control animals progressive tuberculosis that eventually becomes widely disseminated and causes death of the inoculated animals. While some may contend that the virulence of this strain of tubercle bacilli is less than that of recently isolated strains, we are not convinced that this is necessarily true nor do we consider this contention as relevant to the present thesis. The question is what effect, if any, did promin have on a tuberculous infection established by H37RV and not what effect would promin have on other strains of the tubercle bacillus. The latter is of course important but until data have been obtained by suitable procedures no useful purpose is served by insisting that the drug will or will not affect infections induced by

other strains of tubercle bacilli. Second, the fact that sensitivity to tuberculin developed after the injection of the infecting inoculum into the guinea pigs is presumptive evidence that lesions of tuberculosis had become established. Third, the presence at the time of death in all the untreated controls and in many of the treated animals of tuberculosis, with acid-fast bacilli frequently demonstrable, can permit of no reasonable doubt of the virulence of the infecting inoculum. It is true that in a considerable number of the guinea pigs no gross or microscopical lesions of tuberculosis were found, but in every instance such animals had been receiving promin for a considerable time prior to death.

Limitations of the experimental method precluded the possibility of examining minutely every tissue in the search for lesions of tuberculosis. If it had been practical to submit every tissue to a complete scrutiny, it is entirely likely that lesions that escaped detection by ordinary methods would have been discovered. However, it seems improbable that an infective dose of an organism capable of producing a widely disseminated and fatal disease in the untreated animals could have disappeared spontaneously had the animals not been treated. This is of special importance in view of the fact that relatively so little disease was found at necropsy in those groups of animals that did not receive the drug until four and six weeks, respectively, after the infection was introduced. Whether tuberculous infections established in guinea pigs according to our procedure might ultimately regress and finally disappear is unknown. However, in our experience progressive tuberculosis and finally death will occur invariably and this provides reasons for our belief that, unless an extraneous factor is permitted to intervene, the inoculated animals eventually will die as a consequence of the disease induced.

The differences of the disease in the different groups of animals are shown in tables 5 and 6. In table 5 the distribution of lesions of tuberculosis in the visceral organs of predilection is shown. Except for one animal which died six days after inoculation, all the animals in the control or untreated group showed involvement of the spleen, liver and lungs.

Among the 11 animals in the control group lesions were evident grossly in the spleens of 10, in the livers of 10 and in the lungs of 10. In none of the animals did all the visceral organs escape involvement of sufficient severity to be evident grossly. In those few instances in which certain organs contained no gross lesions, subsequent microscopical examination revealed a considerable amount of disease. In the control group the severity of the tuberculous infection was sufficient in all instances to have caused the death of the animals.

Since the tubercle bacilli were injected in all instances into the subcutaneous tissues of the sternal region, the presence or absence of lesions in this situation, as well as in the contiguous lymph nodes, especially those of the axilla, was studied. As may be noted in table 6, lesions of tuberculosis were present in the axillary lymph nodes of 9 and in the subcutis of 8 of the 11 animals in the control group.

When the results of the gross and microscopical examination of the various

tissues and organs of the animals that received promin are compared with the result of similar examinations of comparable material from the animals that did

TABLE 5

Visceral lesions of tuberculosis in different groups of guinea pigs (experiment 2)

GROUP	BEGINNING OF THERAPY IN RELATION TO INFECTION	ANIMALS	TUBERCULOSIS, DETERMINED MICROSCOPICALLY			
			Present			Presumably absent
			Spleen	Liver	Lungs	
1	Controls	12*	11	11	11	0
2	Same day	8	1	1	5	3
3	Three days after	8	3	0	3	3
4	One week after	8	1	0	3	4
5	Two weeks after	8	1	1†	1‡	4
6	Four weeks after	8	3§	0	3‡	5
7	Six weeks after	8	1	0	3	5
8	Two days before	20	3	0	3	15
Total presumably absent.....						39 (57 per cent)

* One animal died after six days.
† Culture of liver was negative for tubercle bacilli.
‡ The peribronchial lymph node in one other animal showed fibrotic tuberculosis.
§ Lesions were minimal in size and calcified.

TABLE 6

Tuberculous involvement of site of inoculation and contiguous lymph nodes (experiment 2)

GROUP	BEGINNING OF THERAPY IN RELATION TO INFECTION	ANIMALS	TUBERCULOSIS; GROSSLY AND MICROSCOPICALLY				
			Axillary lymph node		Subcutis		Animals with visceral lesions
			Present	Absent	Present	Absent	
1	Controls	12*	9	2	8	3	11
2	Same day	8	1	7	3	5	5
3	Three days after	8	3	5	2	6	5
4	One week after	8	3	5	1†	7	4
5	Two weeks after	8	4	4	4	4	4
6	Four weeks after	8	2	6	0	8	3
7	Six weeks after	8	1	7	3	5	3
8	Two days before	20	7	13	3	17	5
Totals (controls not counted).....			21	47	16	52	29 (43 per cent)

* One animal died after six days.
† Small caseous nodule, calcified.

not receive promin, it becomes apparent that (*1*) all the untreated animals were tuberculous, most of them extensively so; (*2*) in 39, or 57 per cent, of the 68

animals that received promin, neither gross nor microscopical evidence of infection in the visceral organs was demonstrated; (*3*) the amount of disease in the 29 treated animals in which tuberculosis was found was, with a few exceptions, of minimal severity; and (*4*) while none of the animals in the control group were without lesions of widely disseminated tuberculosis, 29, or 43 per cent, of the animals that had received promin failed to show lesions of the disease either at the site of inoculation, the contiguous lymph nodes or the spleen, liver or lungs.

These facts supported the belief that there had been an interference with the expected course of the disease in the animals that received promin. The failure to demonstrate lesions of tuberculosis in a considerable number of the animals that were treated and the further fact that the disease in the treated animals was, with few exceptions, minimal and nonprogressive indicate that the action of the drug was significant. That fairly comparable results occurred in the treated animals, regardless of whether the administration of the drug was started before or as long as four or six weeks after inoculation with tubercle bacilli, was surprising and must indicate that the drug was effectively operative against a tuberculous infection in which morbid changes already were established when administration of the drug was started.

Pathological changes in organs of predilection: Group 1: Twelve animals (controls; did not receive promin): The striking and extensive morbid changes that followed the inoculation of untreated guinea pigs with 0.000,5 mg. of strain H37RV provided a satisfactory standard for comparison with the lesions that occurred in the animals that received promin. The tuberculous disease in the control group of animals was comparable in every respect to that which results when guinea pigs are inoculated with a relatively small dose of virulent human tubercle bacilli and are permitted to die as a consequence of the infection. Not only were the spleens extensively affected but tuberculous nodules of variable size occurred in the lungs (frequently associated with hydrothorax) and the liver was the site of moderate to severe disease with multiple infarctions, often an important part of the pathological changes (figure 2).

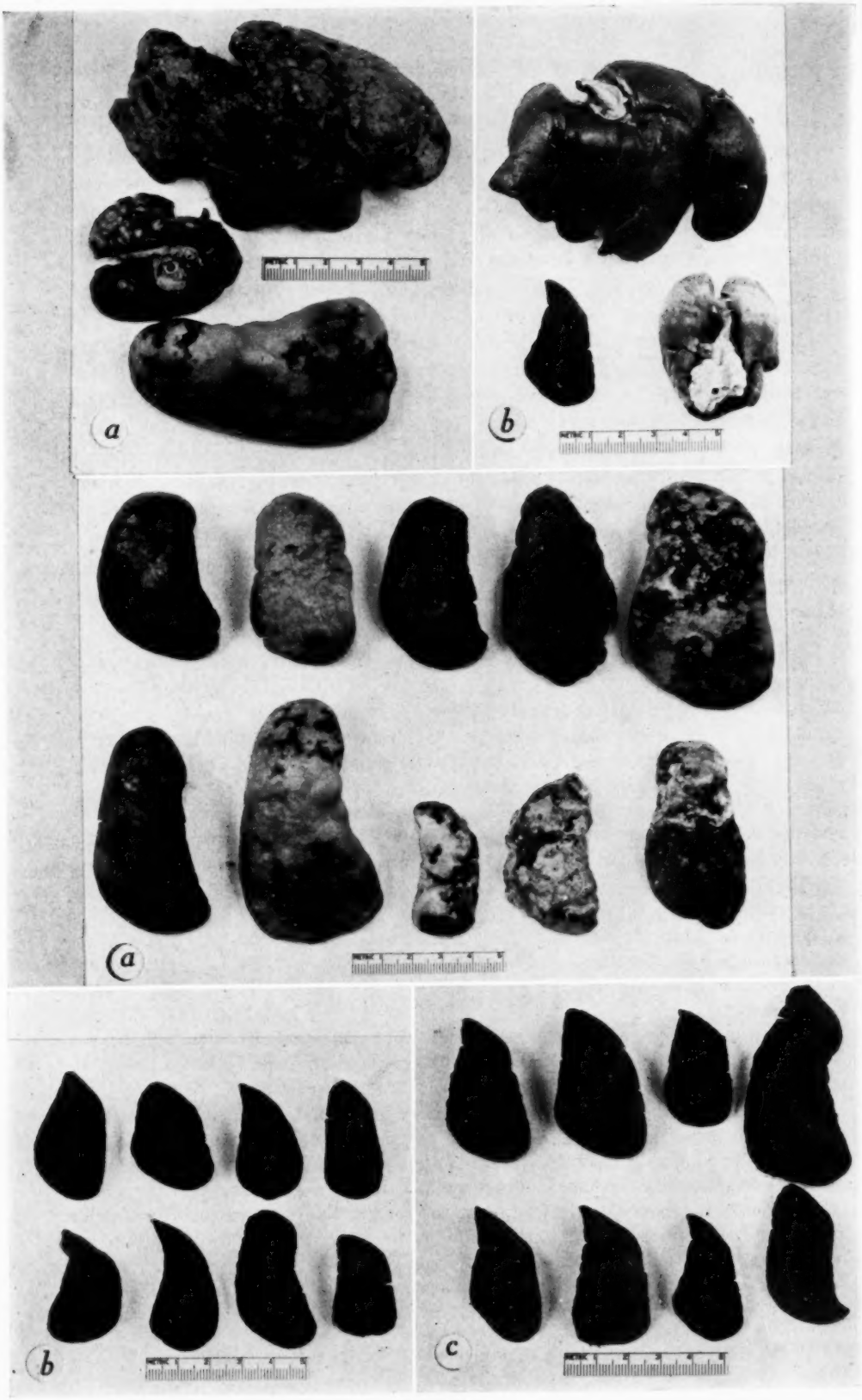
The distribution of the disease in the various situations in the control group of 11 animals[6] was as follows: the liver was affected in 11, the spleen in 11, the lungs were affected in 11, the kidneys in 2, the axillary lymph nodes in 9 and the tissues at the site of inoculation in 8.

Grossly the appearance of the spleens left no doubt of the presence of a severe destructive disease (figure 3). The morbid changes were clearly apparent and the size of the spleens as indicated by their average weight was increased considerably (figure 4).

Microscopically the wide-spread and destructive tuberculous process in the spleen had obliterated in many instances practically all normal anatomical landmarks. Necrosis, usually profound, was a common feature of the splenic lesions and in some instances moderate to severe haemorrhage had occurred. Briefly it may be said that the appearance of the spleen as observed grossly was reflected in the microscopical examination.

As mentioned previously, the lungs of each of the animals in the control group were tuberculous. With the exception of one animal that died sixty-six days after being inoculated, the pulmonary lesions were visible grossly as small translucent foci, as fleshy nodules or as diffuse regions of consolidation, indicative of tuberculous pneumonia. In

[6] Of the original 12 animals in this group one died six days after inoculation.



FIGS. 2–3

the one instance in which the lesions were not seen grossly, both lungs showed microscopically a moderate amount of oedema and large numbers of small to relatively large regions of non-necrotizing epithelioid cells and histiocytes. In the lungs of many of the animals, large and extensive regions were solidified completely (figure 5). Frequently the morbid process revealed an acinar pattern which indicated that the tuberculous changes had been initiated as a tuberculous pneumonia that had embraced a considerable portion of the parenchymal tissue. Necrosis of varying degrees of severity was a common feature of the pulmonary lesions and in 3 instances small foci of beginning calcification were noted. In a few lesions a tendency toward fibrosis was seen. There were noted

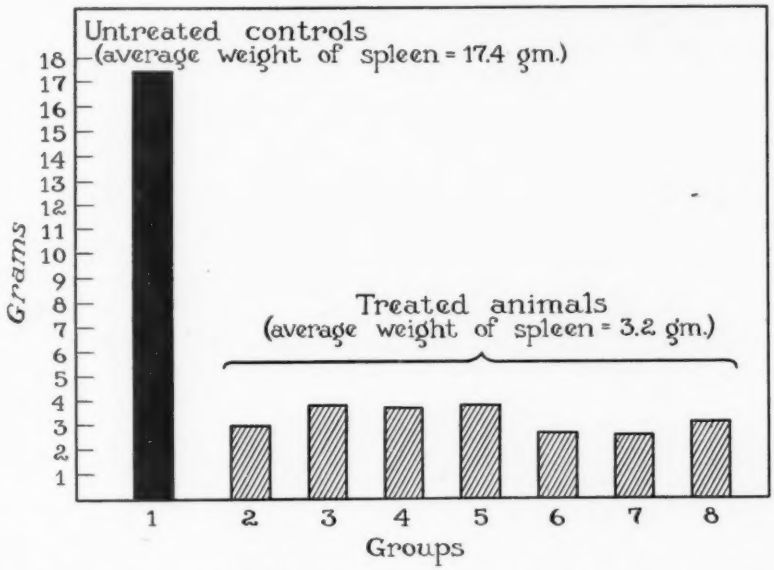


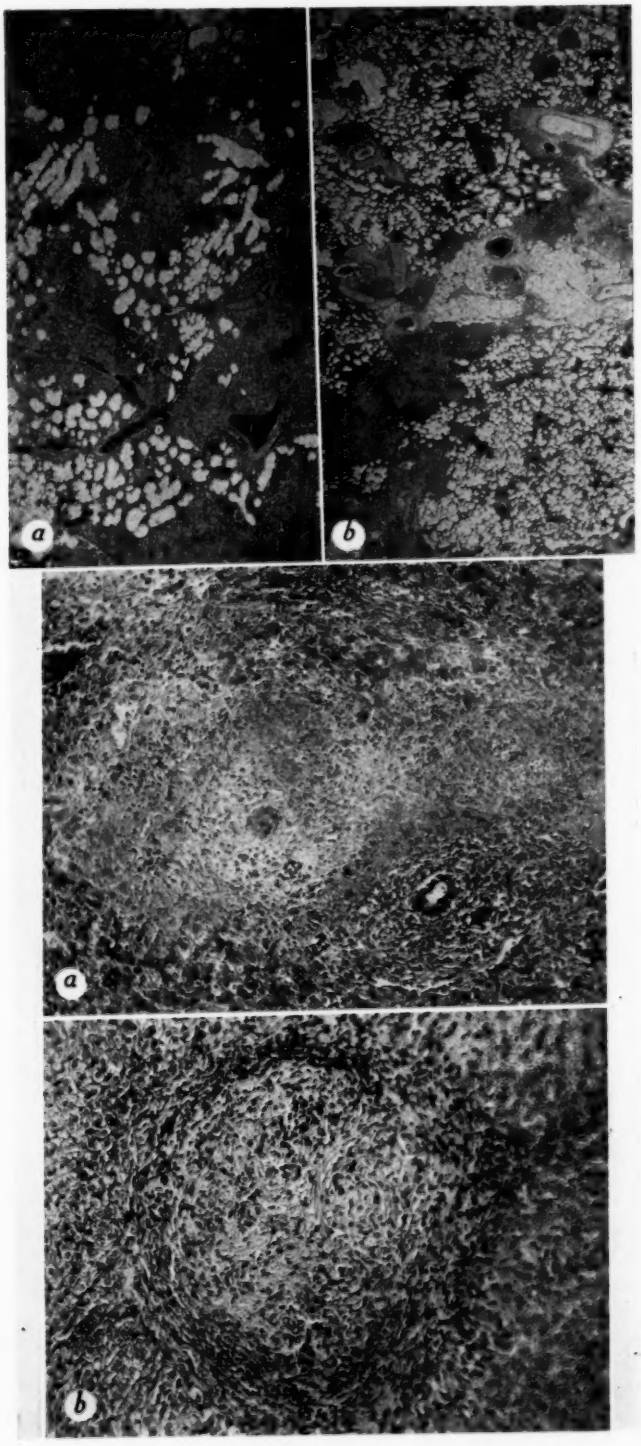
FIG. 4. Comparative weights of the spleens of the treated and the untreated guinea pigs

also a few examples of proliferative endarteritis of uncertain cause, small regions of pulmonary haemorrhage and thrombosis of some of the larger veins. In appropriately stained sections acid-fast bacillary forms were observed in the lesions of all lungs.

In recapitulation, the lungs of all the animals were the site of a severe, progressive and destructive tuberculous disease that with few possible exceptions was of sufficient intensity to have been responsible for the animals' deaths.

FIG. 2 (a) (upper left) Extensive tuberculosis of liver, spleen and lungs of untreated guinea pig that died one hundred forty-five days after inoculation. (b) (upper right) Liver, spleen and lungs of a guinea pig that had been inoculated with tubercle bacilli six weeks before treatment with promin was started. Tuberculosis not visible grossly; microscopic examination also gave negative results.

FIG. 3 (a) (center) Spleens of 10 untreated guinea pigs showing degree of tuberculous involvement. The duration of life after inoculation with tubercle bacilli varied from sixty-six to one hundred eighty-nine days. Compare with *b* and *c*, spleens of two groups of guinea pigs that were treated with promin. (b) (lower left) Inoculated with tubercle bacilli four weeks before treatment was started. Discrete calcified lesions were found microscopically in 3 of the spleens. (c) (lower right) Inoculated with tubercle bacilli six weeks before treatment was started. Lesions were found in only one spleen in this group.



FIGS. 5-6

Tuberculous lesions also occurred in all the livers. Lesions were observed grossly in all the livers except one. In this instance the surface of the organ was definitely roughened and a number of tiny, somewhat indistinct, yellowish granulations were noted. Microscopically this liver was found to contain a moderate number of epithelioid nodules without necrosis. A few giant cells were present and an occasional acid-fast bacillus was seen.

Microscopical examination of the other livers in this group disclosed the presence of an aggravated morbid process. There was severe and extensively distributed advancing tuberculosis with marked destruction of the parenchymal cells and there was noted frequently a wide-spread compensatory or reparative reaction characterized by biliary cirrhosis with an impressive proliferation of newly formed bile ducts. Regions of anaemic and haemorrhagic infarction were prominent features. Softening or necrosis of many of the lesions had occurred (figure 6a) and acid-fast bacilli were demonstrated in the lesions of all but one of the livers.

Group 2: Eight animals (administration of promin started on same day that tubercle bacilli were injected): In this group lesions of tuberculosis were observed grossly in only one animal, although microscopically minimal lesions were found in 4 others. All animals in which lesions were present had survived the entire period of the experiment and were killed one hundred and ninety-two days after being inoculated with tubercle bacilli. In the one animal in which gross lesions were found, the spleen contained numerous discrete nodules measuring approximately 1 mm. in diameter. In this animal the tracheobronchial lymph nodes, the axillary lymph node on the left side and the subcutis at the site of injection also were noted grossly to be tuberculous. Microscopically, lesions also were found in the liver and lungs of this animal. The splenic lesions consisted of conglomerate, hard tubercles some of which were rather extensive. In a few of the lesions minimal necrobiotic changes were evident but no acid-fast bacillary forms were seen. The liver contained a moderate number of well encapsulated tubercles (figure 6b) some of which showed small regions of central necrosis. Foam cells were commonly present. Acid-fast bacilli were not found. The lungs also were affected moderately, the lesions consisting essentially of discrete conglomerate tubercles and epithelioid interstitial or interalveolar pneumonitis. A few acid-fast organisms were discernible.

The other visceral lesions in the guinea pigs of this group were confined to the lungs of 4 animals. The lesions were as follows: in one animal the parenchyma of the lung was the site of an epithelioid or histiocytic type of interalveolar pneumonitis that may or may not have been tuberculous and in addition a minute epithelioid nodule was found in the peribronchial lymphoid tissue; in two other animals a few small epithelioid foci were found; while in the fourth animal the only sign suggestive of tuberculosis was an

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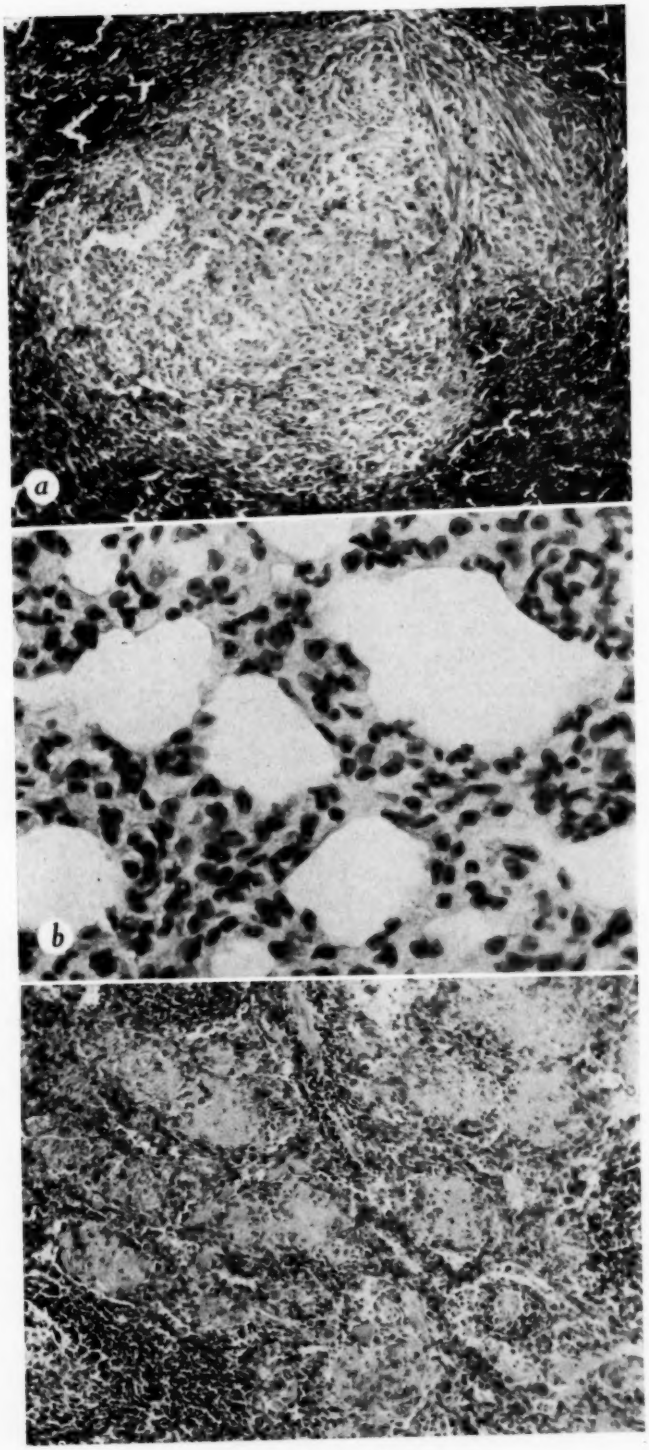
FIG. 5. Comparative amount of tuberculosis in the lungs of one untreated and one treated guinea pig. (a) (upper left) Lung of untreated animal that died seventy-two days after inoculation. There was also present extensive disease in the liver and spleen (× 50). (b) (upper right) Small conglomerate, hard tubercles in one region of lung of a guinea pig that was inoculated with tubercle bacilli two weeks before treatment was started. Animal died one hundred fifty-five days after inoculation (× 50).

FIG. 6 (a). (center) Progressive destructive tuberculous changes in the liver of an untreated guinea pig that died seventy-two days after inoculation with tubercle bacilli (× 120). (b) (lower) Encapsulated tubercle in liver with beginning fibrosis. Treatment with promin was started on the same day that the animal was infected with tubercle bacilli. The animal was killed one hundred ninety-two days later (× 130).



FIGS. 7-8

irregularly outlined diffuse, histiocytic and epithelioid accumulation in a region where the normal lymphoid nodules were hyperplastic.

Although in this group lesions that were probably tuberculous occurred in the lungs of 5 of the 8 animals, the spleen and liver of only one animal were affected. In only one animal were the lesions more severe than minimal. In this animal the lesions of the spleen were visible grossly.

Group 3: Eight animals (administration of promin started three days after inoculation with tubercle bacilli): All the animals in this group were living when the experiment was terminated. In only one were lesions recognized grossly in the visceral organs of predilection, although in another, fibrotic tracheobronchial lymph nodes that were definitely tuberculous were found. In the latter instance subsequent study failed to disclose lesions in the lungs.

Microscopically the spleen in which lesions were seen grossly was found to contain single and conglomerate, hard tubercles. Necrosis had not occurred. Lesions also were found microscopically in 2 other spleens of the animals of this group. In both instances the lesions were few and morphologically comparable to those seen in the spleens first mentioned, being discrete non-necrotizing epithelioid nodules with no signs of progression.

Tuberculous changes were not recognized in the liver of any of the 8 animals.

In 3 animals lesions of the lungs were found microscopically. In 2 the changes were widely distributed although markedly different from the pulmonary lesions seen in the animals in the control group. In the 2 instances mentioned, most of the parenchyma of the lung was involved with interstitial histiocytic and epithelioid pneumonitis. The alveolar spaces were still patent. A few regions were present, however, in which irregularly outlined diffuse regions of consolidation occurred. While some of these changes were not typical of tuberculous lesions, they were considered, however, to be probably tuberculous. Necrosis was not observed nor were acid-fast bacilli found. In the third of the 3 animals in which lesions were found in the lungs, the character of the pulmonary changes was comparable to that described in the first 2 instances except that the involvement was considerably less severe. The changes were essentially those of interstitial pneumonitis with but few regions of consolidation and these of minimal size.

Group 4: Eight animals (administration of promin started one week after inoculation with tubercle bacilli): Six of the animals of this group survived the entire period of observation and were killed one hundred and ninety-two days after being infected with tubercle bacilli. At the time of necropsy the lungs, liver and spleen of all were without gross lesions of tuberculosis. In one there occurred an enlarged mesenteric lymph node that was found to contain conglomerate tubercles with considerable fibrosis in evidence. Microscopically only one of the 8 spleens was affected. In the material examined three small, hard tubercles were found (figure 7a). The lungs of this animal were also found to

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FIG. 7 (a) (upper) Discrete, hard tubercle in spleen of guinea pig. Animal was inoculated with tubercle bacilli one week before administration of promin was started. Animal killed one hundred and ninety-two days after infection (× 110). (b) (center) Interstitial pneumonitis characterized by interalveolar excess of histiocytic cells. Treatment with promin was started one week after inoculation with tubercle bacilli. The lesions in this animal were limited to the lungs (× 480). Tuberculous character of lesions uncertain.

FIG. 8 (lower) Multiple hyalinized tubercles in the spleen of a guinea pig that was inoculated with tubercle bacilli two weeks before treatment with promin was started. Animal died eighty-four days after infection had been introduced (× 110).

contain changes which, although not typical, were considered to be tuberculous. The normal lymphoid nodules of the parenchyma of the lungs were hyperplastic and the spaces between several of them were filled with a diffuse collection of epithelioid cells. Necrosis had not occurred. Wide-spread thickening of the interalveolar septa which was predominantly histiocytic was a notable feature of the pulmonary changes (figure 7b). The lungs of 2 other guinea pigs in this group were found microscopically to be affected in a manner comparable to that just described. The lungs showed interstitial pneumonitis and in one a few discrete, hard tubercles with many lymphocytes at the periphery could be distinguished.

Tuberculous lesions were not found in the liver of any of the animals in this group.

Group 5: Eight animals (administration of promin started two weeks after inoculation with tubercle bacilli): Only 2 animals in this group died during the period of the experiment; the others were killed after one hundred and ninety-two days. Macroscopically the only lesion recognized internally was an enlarged tracheobronchial lymph node which microscopically was found to consist of a hard, conglomerate tubercle with a tendency to fibrosis. Tuberculosis was not found in either lung in this instance. The lungs of only one animal were found to contain lesions microscopically. The changes consisted essentially of a few rather large noncaseating diffuse regions of consolidation, predominantly epithelioid.

The spleen of one animal was found to be affected. The lesions in this instance were somewhat uncommon and quite dissimilar to the usual manifestations of splenic tuberculosis. The animal died eighty-four days after infection, having received promin for seventy days. The only lesions observed at necropsy were a small abscess in the subcutis at the site of inoculation and caseous enlargement of the axillary lymph nodes. Microscopically the visceral changes were limited to the spleen. The splenic nodules were not involved, the lesions being confined to the pulp. The lesions consisted of small discrete nodular units that occurred generally throughout the entire organ (figure 8). Cellular outlines had been obliterated and the respective nodules resembled hyalinized connective tissue structures in which a few atrophic nuclei and a few pale staining erythrocytes could be seen. A finely granular, yellowish brown pigment which probably represented haemosiderin was present.[7] Necrosis had not occurred and acid-fast bacilli were not seen. The homogeneous character of the lesions suggested the possibility of amyloid but a specific stain for this substance gave negative results.

The changes in this instance suggest that a tuberculous process had become established in the pulp spaces, had progressed for a short time and at the time of death was undergoing fibroblastic regression.

Lesions of tuberculosis were found in the liver of only one of the 8 animals in this group. (In this instance a minimal involvement of the lung also had occurred.) In one of two sections of the liver two epithelioid nodules were observed. The lesions were sharply delineated and consisted largely of epithelioid cells many of which were vacuolated (foam cells) and contained pyknotic nuclei. Attempts were made to culture tubercle bacilli from this liver but with negative results.

Group 6: Eight animals (administration of promin started four weeks after inoculation with tubercle bacilli): Three animals in this group had died during the course of the experiment one hundred and twenty-two, one hundred and fifty-nine and one hundred and seventy-six days respectively after receiving the infectious inoculum. At the time of

[7] Specific stain for iron gave a typical reaction for this substance.

necropsy, tuberculosis was not seen in any of the visceral organs, although in one animal hyperplasia of one tracheobronchial lymph node was recorded. Subsequently this was found to represent a necrotizing tuberculous process, but acid-fast bacilli were not demonstrated. Tuberculous changes were not found in the lungs of this animal although a few lesions of minimal size were found in the spleen. Microscopically, somewhat unusual lesions were found in the spleens of 3 of the animals in this group that were living when the experiment was ended. One lesion was found in each of two of the spleens and in the third spleen five lesions were noted. All were essentially similar. They consisted of small circumscribed definitely calcified foci situated within splenic corpuscles (figure 9). Relatively little necrotic material could be recognized. Encapsulation of the lesions was well established. No other signs of a tuberculous reaction were seen in the spleens.

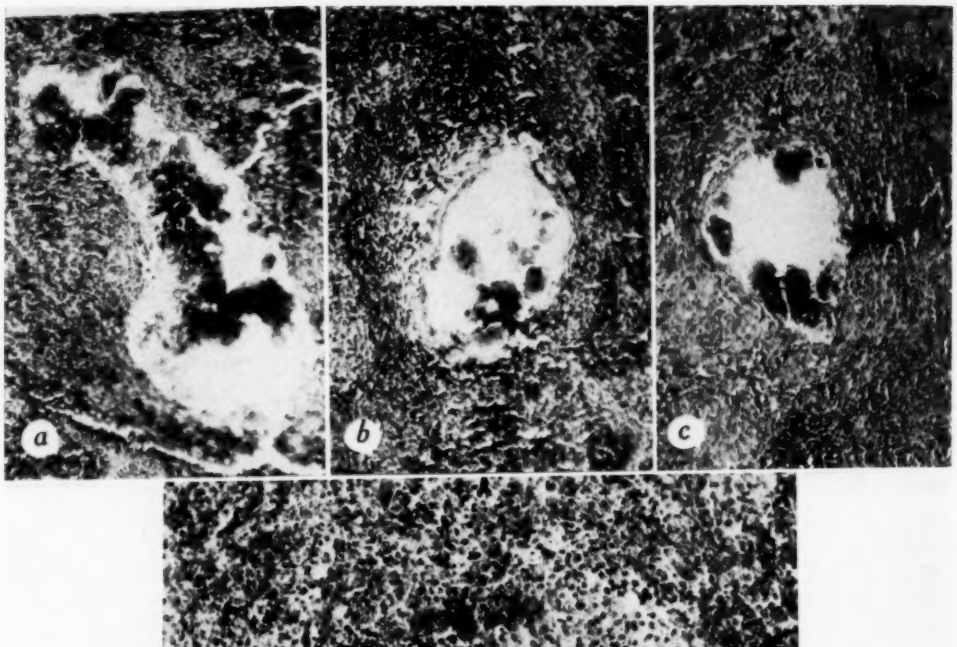
Although acid-fast bacilli could not be demonstrated in the sections in which the splenic lesions occurred, the appearance of the calcified nodules was sufficiently characteristic to justify the belief that they represented residual evidence of a tuberculous infection that was no longer progressive but instead was regressing. That these lesions all occurred in animals that had harbored the infection for four weeks before treatment with promin began appears significant and suggests that even though the disease was definitely established morphologically it finally was altered sufficiently to make further progression unlikely.

Group 7: Eight animals (administration of promin started six weeks after inoculation with tubercle bacilli): All but one of the animals in this group were living at the end of the period of experimental observation. One animal had died sixty-eight days after being inoculated with tubercle bacilli. With the exception of one guinea pig in which the tracheobronchial lymph nodes were considerably enlarged and definitely cirrhotic, no gross evidence of tuberculosis was found. Histological sections showed the presence of tuberculosis in the enlarged tracheobronchial lymph nodes previously mentioned. When examined microscopically, both lungs of this animal also were found to have undergone tuberculous changes.

Microscopical examination revealed tuberculous lesions in the spleen of one animal and in the lungs of 3. The splenic lesions occurred in the animal that died sixty-eight days after infection. This animal had received promin daily for a total of twenty-six days. The lesions in the spleen, which were few, were composed of small nonencapsulated focal accumulations of epithelioid cells (figure 10a). Necrosis had not occurred. Acid-fast bacilli were not observed. Both lungs of this guinea pig also contained a few nonnecrotizing epithelioid nodules. The cytoplasm of many of the epithelioid cells was vacuolated (foam cells) and a few lymphoid cells were present.

The other 2 guinea pigs in which tuberculous lesions were found microscopically in the lungs had been killed when the experiment was terminated. In one, the lesion was minimal in amount and consisted of a few regions of interalveolar epithelioid pneumonitis and two tiny atrophic epithelioid foci in one of the lymphoid nodules of the parenchyma. In the other animal in which pulmonary lesions were observed, although the major portion of the respective lungs was free of recognizable changes, one lung showed a moderate number of conglomerate epithelioid tubercles, in one of which a small region of caseation necrosis was seen (figure 10b). Acid-fast bacilli were not demonstrated.[8] In the opposite lung the changes consisted largely of a histiocytic thickening of the interalveolar septa

[8] As mentioned previously, the tracheobronchial lymph nodes in this animal were also tuberculous.



FIGS. 9–10

with a few diffuse irregular regions of consolidation. While atypical in appearance the reaction was considered tuberculous.

In none of the animals in this group was tuberculosis found in the liver.

Group 8: Twenty animals (administration of promin started two days before infection): In this group only one guinea pig showed grossly visible tuberculous lesions. This animal was one of the 18 survivors of this group. At necropsy, tuberculous lesions were found as follows: two nodules measuring between 2 and 3 mm. in diameter in the spleen; one caseous nodule in each axilla; a tiny granulomatous focus in the subcutis at the site of injection and a cirrhotic enlargement of one of the lymph nodes at the hilum of one lung. In this instance the hilar lymph node was tuberculous, although tuberculous involvement of the parenchyma of the lungs could not be established morphologically. Microscopically, the changes in the spleen were limited to the two nodules that were recognized grossly. The two nodules in which the lesions occurred consisted essentially of conglomerate, hard tubercles.[9] There was no evidence of necrosis. Acid-fast bacilli were extremely few. A few so-called foam cells were noted.

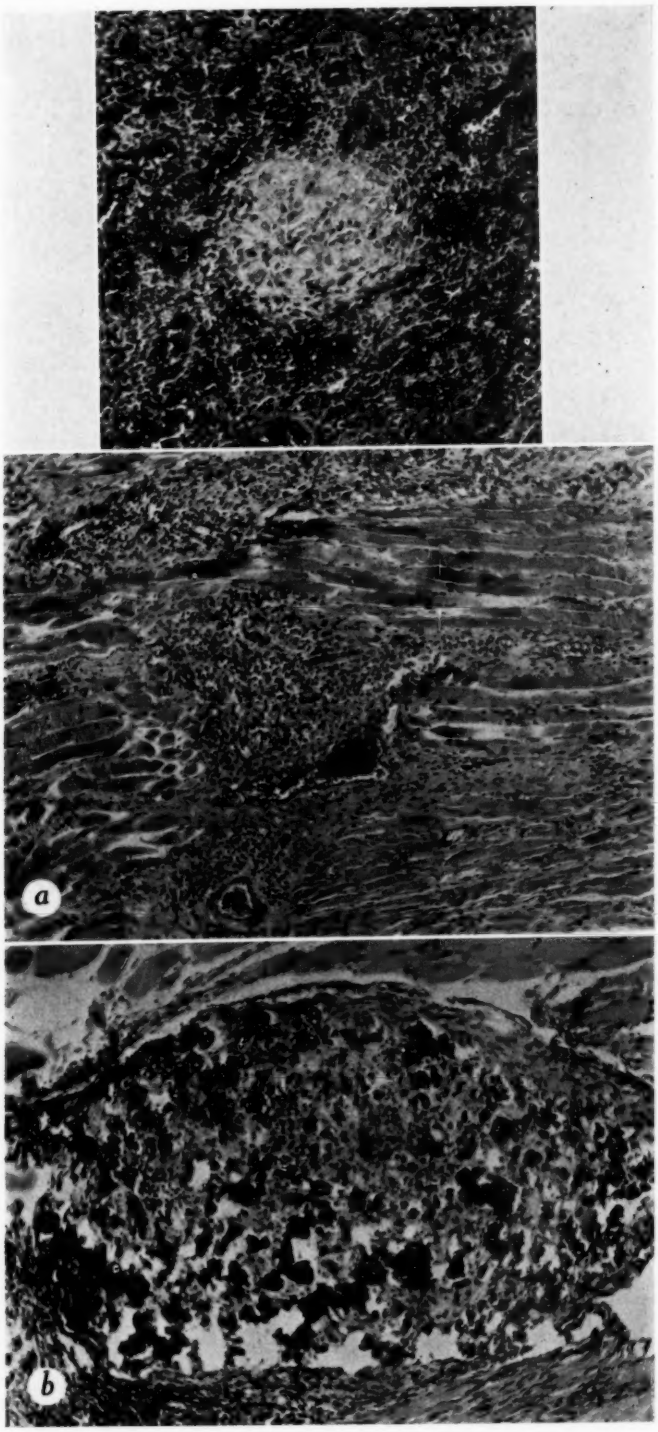
Microscopically the spleens of 3 other guinea pigs in this group showed tuberculous changes. In 2, the lesions found were limited to one hard tubercle of minimal size in each spleen (figure 11) while in the third spleen, which was from an animal that died twenty-nine days after infection, several epithelioid lesions were noted. In the latter many so-called foam cells were present and many lymphocytic forms had infiltrated into the tubercles.

In the lungs of the 20 animals in this group tuberculous changes were found in only 3. In none were the lesions visible grossly. Each of the 3 animals was living when the experiment was terminated one hundred and ninety-two days after injection with tubercle bacilli. The severity of the pulmonary involvement varied in the 3 animals from minimal to moderate and in each instance both lungs were affected similarly. The minimal lesions consisted either of discrete, compact foci of epithelioid cells and histiocytes with no signs of necrosis or of irregular diffuse regions of consolidation, associated peripherally with an epithelioid or histiocytic type of interalveolar pneumonitis. In the lungs in which the reaction was more severe, the lesions were predominantly diffuse and fairly exten-

[9] This term is used by Rich (11) and by Rich and McCordock (12) to denote small, discrete, sharply delineated, irregular or spherical, compact masses of epithelioid cells often surrounded or infiltrated by small lymphocytic cells. For an admirable consideration of the significance of "hard" and of "soft" tubercles in the pathology of tuberculosis the paper by Sabin (13) may be consulted.

FIG. 9. Circumscribed calcified lesions in spleens of 3 guinea pigs inoculated with tubercle bacilli four weeks prior to beginning of treatment with promin. (a) (upper left) In addition to two calcified nodules in the spleen one peribronchial lymph node also was affected; (b) (upper center) recognizable signs of tuberculosis limited to the one nodule in the spleen; (c) (upper right) in this animal one small tuberculous nodule was also found in one lung. All magnifications 110 diameters.

FIG. 10 (a) (center) Area of epithelioid reaction in spleen of guinea pig. Treatment with promin was started six weeks after inoculation with tubercle bacilli. Animal died after receiving promin for twenty-six days (×160). (b) (lower) One of several epithelioid nodules near periphery of lung of a guinea pig that was inoculated with tubercle bacilli six weeks prior to the beginning of treatment. Animal killed one hundred and ninety-two days after inoculation (× 35).



FIGS. 11–12

sive in distribution. Discrete tubercles were not seen nor was necrosis recognized. So-called foam cells were numerous and mitotic divisions of histiocytes were noted occasionally. The thickening of the interalveolar septa by epithelioid and histiocytic elements was a prominent feature. Acid-fast bacilli were not found in any of the lesions of the 3 animals in which there were pulmonary changes.

The lesions just described were markedly dissimilar to the lesions of the lungs of the animals in the control group. In the latter, the involvement was far more extensive and the character of the reactive process was that of a progressive destructive disease with necrosis a prominent feature. In none of the treated animals of this group were tuberculous lesions found in the liver.

Pathological changes in lesions at site of inoculation and of contiguous lymph nodes: As mentioned previously, morbid changes were present in the tissues at the site of inoculation and in the contiguous (usually axillary) lymph nodes of many of the animals in the control group and in a number of the animals that received promin (table 6). At the time of necropsy the percentage of lesions in these situations in the control group was greatly in excess of that in the treated animals. Furthermore, significant differences also were recognized in the severity of the morbid changes in the untreated and the treated animals. These differences were definitely apparent when the material was examined microscopically.

Site of injection: In the controls, lesions in the subcutis that could be recognized grossly occurred in 8 of the 11 animals.[10] Generally speaking, the lesions consisted of diffusely infiltrating caseous nodules in which extension into the hypoderm was fairly common (figure 12a). Necrosis was a prominent feature of the lesions. In one instance an open ulcer had persisted. In a few instances small calcified foci were present among the caseated debris of the lesion. In only one animal was the lesion of the subcutis circumscribed. The appearance of most of the lesions indicated a necrotizing advancing process.

In the 68 treated animals lesions were found in the subcutis in only 16. While a few exceptions were noted, the morbid process in most instances consisted of definitely encapsulated foci of caseation necrosis, in some of which calcification of varying degrees had occurred (figure 12b). So-called daughter tubercles or other signs of peripheral extension were infrequent. In most of the treated animals the initial lesion appeared to be static or at least nonprogressive.

Axillary lymph nodes: Among the 11 animals in the untreated group, the lymph nodes in one or both of the axillae of 9 were tuberculous. While minor differences in the degree

[10] One of the original 12 guinea pigs had died prematurely.

FIG. 11 (upper) One small, hard tubercle in spleen of guinea pig in which the administration of promin was started two days before the animal was inoculated with tubercle bacilli (× 150).

FIG. 12 (a) (center) Extension of tuberculous process into the musculature contiguous to site of subcutaneous inoculation of tubercle bacilli in untreated guinea pig. Animal died seventy-two days later (× 80). (b) (lower) Caseocalcareous encapsulated nodule in the subcutis at the site of injection with tubercle bacilli. Animal was inoculated two weeks before treatment with promin was started and was killed one hundred and ninety-two days after being infected (× 80).

of involvement of the lymph nodes in the respective animals were noted, in general the disease was severe and progressive. In many instances the normal lymphoid structures were nearly or completely destroyed by the advancing tuberculosis. Caseation necrosis was the most constant feature, although in a few instances fibrotic changes were prominent. A few small foci of calcification also were seen.

Of the 68 animals that received promin, tuberculous adenitis affecting the axillary lymph nodes was recorded in 21. While in many the degree of involvement was considerable, the lesions differed in one important respect from those in the animals that did not receive promin. Whereas in the latter the disease process was advancing and was characterized by wide-spread caseation necrosis, with a few exceptions the process in the treated animals was associated with minimal or no recognizable necrosis but was characterized instead by the large amount and dense character of the fibrous connective tissue that was present. That in most instances the disease had infiltrated throughout considerable portions of the lymph nodes was evident. But it was likewise apparent that at the time of necropsy the progression of the process had been halted or at least retarded and cirrhosis rather than necrosis was the predominant feature. The reverse was true in the axillary nodes of the animals that had not received promin.

COMMENT

This study, while admittedly limited in scope, perhaps has yielded a few new facts concerning tuberculosis that may provide an impetus for additional work on a phase of the disease in which the results have been for the most part of academic interest only or entirely disappointing. We have no illusions as to the enormity of the problem or as to the many pitfalls that abound for the unwary. We have tried to base this report on the facts revealed and have attempted at all times to apply a proper restraint to impulses that might engender an attitude of uncritical enthusiasm. In this spirit we have assembled the data with care and have attempted to interpret the results conservatively.

Among the facts established are the following. (*1*) The strain of tubercle bacilli used to infect the guinea pigs is of at least standard virulence and in the dosage used is capable of initiating a progressively destructive experimental tuberculous disease that is eventually lethal. This is an extremely important point in work of this kind. We chose H37RV because its biological characteristics are well known and because of its dependable pathogenicity under the conditions of proper cultivation. Many other strains might have served equally well but it seems important in work of this kind that so far as possible the infective inoculum be standardized. This should obtain at least until preliminary observations have established facts that warrant an expansion of the investigation.

(*2*) The oral administration of promin influenced the expected results of a disease process which, when permitted to proceed without intervention, eventually becomes widely disseminated and of sufficient severity to terminate the life of the animal. This statement is warranted from the data obtained, which established that the animals that received promin lived longer than those that did not receive promin; and perhaps of greater importance, the disease in the treated animals not only was less but was impressively different in char-

acter. Whereas in the untreated animals the infection had expressed itself as an aggressively destructive, complicated morbid process, the recognizable disease in most of the animals that received promin was a process that was comparatively simple in structure and static or regressive. That 29, or 43 per cent, of the 68 animals that had received promin were without demonstrable lesions of tuberculosis seems significant.

(*3*) The favorable effect of promin apparently was realized regardless of when the administration of the drug was started in relation to the duration of the infection. This has important implications. That all the animals in the treated groups presumably were infected with tubercle bacilli may be inferred from the positive results of the tuberculin tests and from the fact that in 39, or 57 per cent, of the 68 animals that received promin residual morphological signs of the infection were demonstrated. Therefore, it is a reasonable assumption that, in those instances in which treatment was delayed from four to six weeks after the animals had received tubercle bacilli, the disease had become definitely established before treatment was started and that promin provided an unfavorable situation for the natural progression of the infection.

What the mechanism may be that is responsible for the favorable action of promin on an incipient tuberculous infection or in preventing lesions from forming is uncertain. Corper, Cohn and Bower (14) expressed the belief that sulfanilamide and sulfapyridine modified the lesions of experimental tuberculosis by suppressing the mononuclear hyperplasia that naturally follows infections with tubercle bacilli in a susceptible animal. The retardation of the production of mononuclear cells or histiocytes consequently would interfere with or prevent the formation of tubercles without having exerted directed action on the tubercle bacilli. According to their belief the two drugs mentioned exerted an "organic toxic" or "leucotoxic" effect only and thus there resulted an apparent rather than a true retardation of the tuberculous infection.

From a careful examination of the tissues obtained from the animals that received promin, we have been unable to demonstrate morphological changes that would indicate that toxic substances had been operative on the parent cell from which the cellular response to tubercle bacilli is derived. The aplastic changes described by Corper, Cohn and Bower as occurring in the spleens of animals receiving sulfanilamide and sulfapyridine have not been recognized in our material. It was generally true that haemosiderosis occurred and that the vascular spaces of the splenic pulp were markedly congested, but there was no discernible evidence of retrogression of the cellular elements of the pulp cords (figure 13).

Certain facts that were revealed from the study of our material indicate that the influence of the promin has been expressed by direct or indirect action against the tubercle bacilli. Exactly how this action is exerted is problematic. Evidence in support of the hypothesis of direct or indirect action consists of the following:

1. Quantitatively and qualitatively, there were present at least in the spleens

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1. Quantitatively and qualitatively, there were present at least in the spleens

of the animals that received promin, potential cellular elements from which an anatomical reaction could and sometimes did develop.

2. The structural character of the reaction in those instances in which lesions occurred was indicative in most instances, not only in the spleen but also in the other organs, of a process that was static or regressive rather than progressively destructive. This suggests that the resistance of the host had been made more effective by a degradation of the virulence of the infective agent.

3. Unless the drug had a direct or an indirect action on the tubercle bacilli, it is difficult to account for the regressive changes that occurred in the lesions,

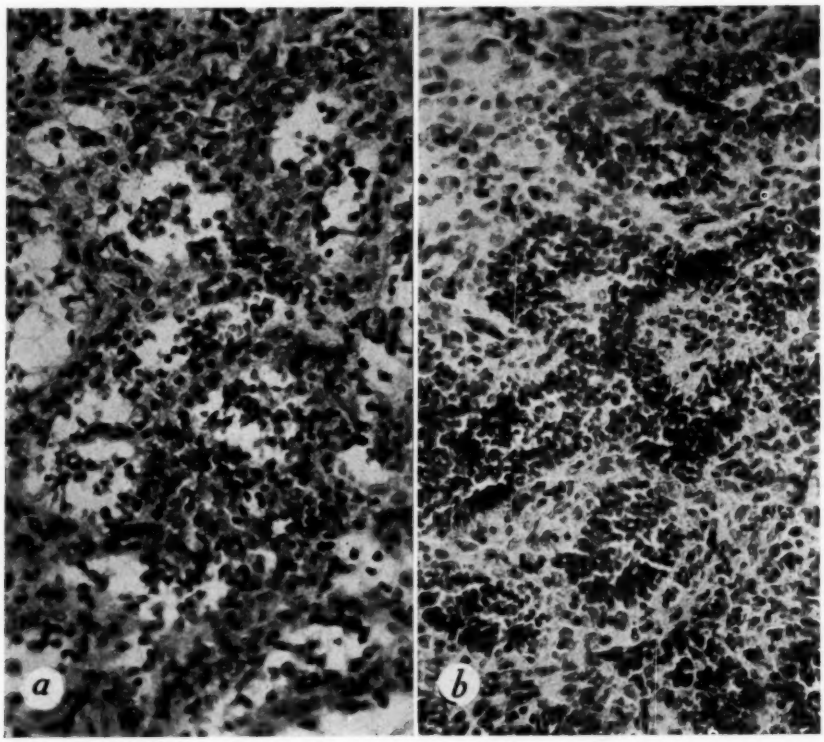

FIG. 13. Relative amounts of pulp tissue in spleen of, (a) normal guinea pig and (b) guinea pig that had received promin daily for one hundred and ninety-two days. Note the abundance of intervascular elements in the latter. Both magnifications, 275 diameters.

especially those of the animals in which treatment with promin was started four and six weeks after inoculation with tubercle bacilli. Obviously the effect of the drug in these latter instances was exerted after rather than before the cellular response to the infection was initiated. In some instances at least, the lesions persisted but had regressed in a manner characteristic of a tuberculous lesion that is sterile or in which the bacteria are no longer capable of overcoming the resistance of the host.

4. The fact that the suspensions prepared from 8 of 17 spleens from previously infected guinea pigs (experiment 1), that had received promin for varying periods,

failed after eight weeks to establish in normal guinea pigs recognizable lesions of tuberculosis seems to constitute reasonably good evidence that in those instances no virulent bacilli were present in the spleens from which the suspensions were made. It should be noted also that tubercle bacilli were demonstrated by this reinoculation experiment in the spleens of a few treated animals, even though treatment had been discontinued for nearly three months. This suggests the possibility of development of some form of acquired immunity. That the bacteria were sufficiently virulent to produce lesions of tuberculosis in previously normal guinea pigs was demonstrated on subinoculation.

SUMMARY

Two experiments are described in which the effect on experimental tuberculosis of an organic compound called "promin," designated chemically as sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate, was determined. The drug was administered orally with the feed, which contained 1 per cent of promin by weight. In the first experiment 50 guinea pigs were used. Thirty received the drug for two days before the tubercle bacilli were introduced and daily thereafter. The remaining 20 guinea pigs did not receive the drug. Although a nutritional disturbance introduced a complicating factor into the first experiment, the results indicated that promin had had a deterrent effect on the course of the disease. When the last of the controls died eighty-two days after being inoculated with tubercle bacilli, 24 of the animals that had received promin were living. Promin was removed from the diet of 12 of the 24 survivors, while the drug was continued in the diet of the remaining 12. The experiment was terminated eighty-two days later at which time 13 animals were living, 8 of which had not received promin during the last eighty-two days of life. Although lesions of progressive tuberculosis were present in the organs of predilection of all the animals of the control group, the degree of tuberculous involvement in the animals that received promin was notably less. Fewer situations were affected and the lesions were fewer and smaller than in the guinea pigs that were untreated. Furthermore, in the spleen, liver and lungs of approximately 50 per cent of the treated animals no cellular reactions that could be considered tuberculous were observed either grossly or microscopically.

The objectives of the second experiment were to confirm if possible the results of the first experiment and to determine if promin would have an effect on tuberculous infections introduced at the same time or at varying periods before treatment with promin was begun. Eighty guinea pigs were used. Twelve did not receive promin and 48 of the remaining animals were divided into six groups of 8 animals each. In these six groups beginning of administration of promin in relation to the time of infection was as follows: day of infection, three days after, one week after, two weeks after, four weeks after and six weeks after. In 20 animals the administration of promin was started, as in the first experiment, two days before the animals were inoculated with tubercle bacilli. At the expiration of six months all the untreated animals were dead, presumably as a result of the severe and widely disseminated tuberculous infection, while

only 11, or 16 per cent, of the treated animals had died during this period. Fifty-seven, or 84 per cent, of the treated animals survived. Among the 68 animals that had received promin, demonstrable lesions of tuberculosis in the liver, spleen and lungs were absent in 39, or 57 per cent, while no lesions were found in the visceral organs of predilection, at the site of injection or in the contiguous lymph nodes in 29, or 43 per cent, of the treated animals. It is concluded that under the conditions of the two experiments described promin had a deterrent effect on experimental tuberculous infection.

SUMARIO

Descríbense dos experimentos en que se determinó el efecto sobre la tuberculosis experimental de un compuesto orgánico llamado "promina," cuya designación química es sodio p,p′-diaminodifenilsulfona-N,N′-sulfonato de bidextrosa. Esta droga fué administrada por vía bucal con la alimentación, que contenía 1 por ciento de promina por peso. En el primer experimento se utilizaron 50 cobayos: 30 recibieron la droga por espacio de dos días antes de introducir los bacilos tuberculosos, y a diario después. Los otros 20 no recibieron la droga. Aunque un trastorno nutritivo introdujo un factor complicador en el primer experimento, el resultado indica que la promina ejerció un efecto contrario a la evolución del mal. Al morir el último de los testigos 85 días después de inocularles bacilos tuberculosos, estaban vivos 24 de los animales que habían recibido promina. La promina fué eliminada de la alimentación de 12 de los 24 sobrevivientes, continuándose en los otros 12. El experimento terminó 82 días después, para cuya fecha estaban vivos 13 animales, 8 de los cuales no habían recibido promina en los últimos 82 días. Aunque había lesiones de tuberculosis evolutiva en los órganos de predilección de todos los animales del grupo testigo,la invasión tuberculosa en los animales que recibieron promina fué decididamente menor. En ellos también había menos sitios afectados, y las lesiones eran más escasas y menores que en los cobayos dejados sin tratar. Además, en el bazo, hígado y pulmones de 50 por ciento de los animales tratados no se observaron ni macroscópica ni microscópicamente reacciones que pudieran considerarse tuberculosas.

Los objetivos del segundo experimento fueron confirmar, si era posible, el resultado del primero, y determinar si la promina ejercía algún efecto en las lesiones tuberculosas introducidas al mismo tiempo o en períodos variables antes de iniciar la prominoterapia. Se emplearon 80 cobayos: 12 no recibieron promina, y los otros 48 fueron divididos en seis grupos de 8 animales cada uno. En estos seis grupos se inició la administración de promina en relación con el período de infección en la forma siguiente: día de la infección; tres días después; una semana más tarde; dos semanas después; cuatro semanas y seis semanas más tarde. En 20 animales se inició la administración de promina, lo mismo que en el primer experimento, dos días antes de inocular en los animales los bacilos tuberculosos. Al cabo de seis meses todos los animales sin tratar estaban muertos, presuntamente a consecuencia de la intensa y diseminada infección tuberculosa, mientras que sólo habían muerto 11, o sea 16 por ciento, de los

tratados. De éstos sobrevivieron 57, o sea 84 por ciento. Entre los 68 animales que habían recibido promina no había lesiones demostrables de tuberculosis en el hígado, bazo o pulmones en 39, o sea 57 por ciento, mientras que no se encontraron lesiones en los órganos viscerales de predilección, en el sitio de la inyección o en los ganglios linfáticos contiguos en 29, o sea 43 por ciento, de los animales tratados. De lo anterior dedúcese que en las condiciones de los dos experimentos descritos, la promina ejerció un efecto inhibidor sobre la infección tuberculosa experimental.

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SURVIVAL OF TUBERCLE BACILLI[1]

The Viability of Dried Tubercle Bacilli in Unfiltered Roomlight, in the Dark and in the Refrigerator

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Some time ago, in consideration of the chances of infection of employees and reinfection of negative patients, we examined the rooms and immediate surroundings of positive patients at Barlow Sanatorium for viable tubercle bacilli. Cultures were made from swabbings of bed-side tables, lamps, bed frames and other articles frequently handled; from room dust and sweepings; and from cotton filters through which room air had been sucked. Uniformly negative results led to speculation as to the effect of daytime roomlight on living tubercle bacilli and its rôle in preventing infections. Daylight and sometimes sunlight enters the rooms under consideration in abundance, for the most part unfiltered by glass and passing only through wire screen. The following experiments represent an attempt to determine the importance of such light in rendering tubercle bacilli nonviable and noninfectious.

Most of the work on the viability or longevity of tubercle bacilli under varying conditions was done before the first World War. Rosenau (1) and Corper and Cohn (2) have published reviews of the literature. The present state of our knowledge is well summarized by Park and Williams (3):

> "Tubercle bacilli in sputum when exposed to direct sunlight are killed in from a few minutes to several hours according to the thickness of the layer and the season of the year. They are usually destroyed by diffuse daylight in from five to ten days. Dried sputum in rooms protected from abundant light has occasionally been found to contain virulent tubercle bacilli for as long as ten months."

As far as I know, the longest survival on record of human and bovine tubercle bacilli is twelve years in paraffin-sealed broth cultures kept continuously in the incubator as reported by Corper and Cohn (2) in 1933. Interestingly enough only 0.01 per cent of the human bacilli were still viable and none was recovered from broth of pH less than 6.1 or more than 7.6. According to Vidal (4) tubercle bacilli in moist sputum kept at 2°C. and protected from the light were still viable after twelve months. Tubercle bacilli suspended in physiological saline and kept in the refrigerator were found to be alive after three hundred twenty-five days by Shope (5) in 1926; after eight hundred days by Pugnani (6) in 1930; and (a bovine strain) after four hundred fifty days at a temperature of 5° to 10°C. by Feldman (7) in 1932.

Reports on the viability of tubercle bacilli in the dark vary considerably.

[1] From the Barlow Sanatorium, Los Angeles, California.

In 1905 Twitchell (8) found that moist tuberculous sputum kept in paraffin-sealed bottles in the dark was still infectious for guinea pigs at one hundred seventy days but not at one hundred eighty-eight days. On the other hand, sputum folded in a handkerchief or blanket and so, presumably, quickly dried, was infectious at seventy but not at one hundred ten days. Arms and Wade (9) in 1912 dried tuberculous sputa of different sources on pieces of tongue depressors and kept them in the dark. Animal inoculations made at frequent intervals showed a bacillary survival of from less than four weeks in the summer to as long as eighteen weeks in the winter, depending on the strain. In 1917 Soparker (10) reported dried tuberculous sputum kept in a dessicator in the dark to be still infectious for guinea pigs after three hundred nine days, but moist sputum kept in a closed test tube to be noninfectious after only twenty-six days. Vidal (4), in 1934, wrote that tubercle bacilli in sputum protected from the light and kept at 20°C. were still alive at four months. That deprival of water and oxygen *per se* does not kill tubercle bacilli was shown by Potter (11) in 1937. Avian bacilli were stored in the dark, at room temperature and at 37°C., in glass tubes from which water and oxygen were exhausted as completely as possible by physical and chemical means. Culture and inoculation proved the microörganisms to be still alive after twelve months, fourteen months and even two years.

The rapid lethal effect of direct sunlight on tubercle bacilli has been recognized by numerous observers from 1890 onward. Recently Zink (12) published evidence indicating that, although this is mostly attributable to ultraviolet radiations, it may be due partly to the high temperatures developed on surfaces exposed to the sun. Ultraviolet radiations from mercury vapor lamps may kill tubercle bacilli in suspensions or dried smears in from three to ten minutes according to Mayer and Dworski (13), Howze (14) and Edinow (15). Edinow showed that lamp radiations were ineffective when filtered through glass.

Numerous reports on the viability of tubercle bacilli in "diffuse" daylight or in roomlight usually fail to describe the exact conditions of the experiment and the quality of the diffuse light. In other cases the light in question was filtered through the windows of the room or the bacillary preparation was exposed through the walls of a glass container. Cornet (16), in 1904, successfully infected guinea pigs with the dust from a room six weeks after the death of its tuberculous occupant. Twitchell (8) reported that sputum on a carpet "under ordinary room conditions" was still infectious at thirty-nine but not at seventy days. Soparker (10) placed tuberculous sputum in watch glasses covered with wire gauze near an open window so that it was fully exposed to daylight but protected from direct rays of the sun. The tests were carried out in India during the month of February. The sputum was capable of infecting guinea pigs after six but not after eight days of exposure. Tuberculous sputum spread in films 1.4 mm. thick and exposed to diffuse light in a sanatorium room with "open balcony" facing south in July, 1935 near Toledo, Spain, was found by Blanco and Ondovilla (17) to be positive by inoculation after twenty-five but negative after twenty-eight days.

The amount of bactericidal radiation from the sky, the source of daytime roomlight, varies according to the time of year, the latitude, the time of day and the altitude. Ives and Gill (18) measured radiations for wave lengths less than 313 millimicra (3130A°) under clear skies in several cities of the United States. For the months of February, April and August, representative readings at noon in microwatts per sq. cm. were: Los Angeles, 29.7, 77.3 and 66.4, respectively; a group of northern cities (average readings), 12.8, 70.2 and 74.6, respectively. In Los Angeles, the ultraviolet radiations at 9:00 a.m. and 3:00 p.m. were about one-third as intense as those at noon in the wintertime and about one-half in summer. Like ratios for the northern cities were about one-tenth in winter and one-half in summer. At an altitude of 7,000 feet ultraviolet radiations are increased some 40 to 50 per cent over those at sea level, according to Coblenz and Stair (19). Other factors influencing ultraviolet rays from the sky are the amount of ozone in the upper atmosphere, sunspots, clouds and air pollution (18, 19). The amount of cloudiness varies greatly. Some clouds may by reflection even increase sky shine (18). The data of Ives and Gill show that with 10/10, or complete cloudiness, radiations at Los Angeles are diminished roughly one-third to one-half. The diminution was somewhat greater in northern cities. Smoke and dust, of course, diminish sky radiation in greatly varying degree. Smoke and dust are, in turn, diminished by wind and by low relative humidity (18).

PROCEDURE

Suspensions of virulent human tubercle bacilli in water or in sputum were spread on cover slips in 0.05 cc. amounts and allowed to dry. Some of these preparations were placed in a small unheated room in the light of an unglazed but screened north window through which the sun was known never to shine; others were kept in complete darkness within a cardboard box inside a second such box which in turn was kept in a table drawer of an unheated room. At intervals, cover slips were removed and shaken vigorously with a weak alkaline solution so as to separate the dried film and mobilize the bacilli for culture and animal inoculation.

The microörganisms tested had been previously isolated in this laboratory from sputum, typed and subcultured on Petragnani's medium. One strain, identified as no. 24, was used only in the first experiment; the other, no. 88, in all the remaining studies.

Suspensions were prepared after the method of Corper (20) in a centrifuge tube by grinding, with a glass rod, weighed amounts of moist colonies that had been grown four to eight weeks on Petragnani's medium. First moisture was made with 2 drops of M/15 K_2HPO_4 and suspension completed with distilled water. Progressive dilutions were made by mixing 1 cc. of one suspension with 9 cc. of water, using a fresh pipette for each transfer. Sputum suspensions were obtained by shaking for twenty minutes in a machine 1 cc. of the proper water suspension with 9 cc. known negative sputum. Smears were made with a pipette so as to cover two-thirds to three-fourths of the surfaces of 22 mm. glass squares. The preparations were arranged on a table 8 inches below and 20 inches in from a window which was 32 inches high by 20 inches wide, so that the space occupied was just less than the width of the window and about half its height. The amount of daylight entering was restricted by 3-foot eaves at a level of 4 feet above. Sterile forceps were used to remove cover slips to 4 oz. bottles containing 7 cc. of a 0.25

per cent solution of sodium hydroxide. The bottles were shaken ten minutes by a machine with a rate of 240 vibrations per minute and a displacement of 3 inches. When the material was to be cultured, half the liquid was mixed with an equal quantity of 2.5 per cent oxalic acid; both halves were centrifuged at high speed for ten minutes and the sediments each planted on 2 tubes of Petragnani's medium, 2 drops to a tube. For guinea pig inoculation, the entire alkaline digest from one cover slip was centrifuged, washed and injected subcutaneously. Cultures were observed for two months. Clinically positive guinea pigs were autopsied at one month, all others at two months. Gross or microscopical evidence of visceral tuberculosis was required as proof of living tubercle bacilli.

The United States Weather Bureau at Los Angeles, from which meteorological data were obtained, is within two miles of and at about the same altitude as the site of the experiments.

RESULTS

In the first experiment, smears were prepared from suspensions containing 0.001 and 1.0 mg. tubercle bacilli per cc., respectively, so that the total amount of bacilli per smear was either 0.000,05 or 0.05 mg. Exposures were made during a clear dry period in mid-winter. The relative humidity varied from 17 to 62 per cent, the temperature from 45° to 76°F. Recovery was by culture. As shown in table 1, the microörganisms survived a maximum of four days, that is, exposure to forty hours of daylight. There was heavy growth from both smears containing the greater dosage (0.05 mg.) at one day, while at four days only the sputum smear was positive and then in a minimal degree. All cultures were negative at twelve days. Growth from the smears of the lesser dosage (0.000,05 mg.) diminished rapidly and was barely demonstrable at four hours in case of the sputum and at one day in the case of the water preparation.

In this experiment, tubercle bacilli in sputum smears were found to be stainable and fully acid-fast after three months' exposure to roomlight. Elsewhere we found well stained acid-fast bacilli after five months, although in that case the proportion of stainable rods was diminished.

A second experiment was carried out to compare the viability of dried tubercle bacilli in roomlight and in complete darkness. Smears were prepared from water and sputum suspensions containing 0.1 mg. bacilli per cc. so that the dose per smear was 0.005 mg. The test was run in the early spring during cloudy and even rainy weather (table 2). Bacilli were recoverable by culture at one day, that is, after exposure to twelve hours of light, not at two days. In the dark they were recoverable at nine days, not at forty. There was no demonstrable difference between viability in sputum and water preparations.

A third set of tests was run in mid-summer (table 3). To improve chances of recovery, suspensions containing relatively huge quantities of microörganisms, that is, 10 mg. per cc., were employed, so that the dose per smear was 0.5 mg. The preparations were exposed to both roomlight and dark. Guinea pig inoculation as well as culture was used for recovery. The average cloudiness during the first few days was five-tenths and the sunshine about two-thirds of possible. Living tubercle bacilli were demonstrable after fifty-one and one-half hours in

roomlight (thirty-one and one-half hours of actual daylight) and fifty-five days in the dark. In roomlight, both culture and guinea pig were positive at fifty-one and one-half hours (thirty-one and one-half hours of daylight), culture

TABLE 1

Exposure of dried tubercle bacilli to roomlight

Recovery by culture

Exposure started at 12:00 noon

DATE, 1936	WEATHER*	SUNSHINE PER CENT OF POSSIBLE*	TIME ELAPSED	HOURS OF DAY-LIGHT†	WATER SMEAR		SPUTUM SMEAR	
					0.000,05 mg. T.B.	0.05 mg. T.B.	0.000,05 mg. T.B.	0.05 mg. T.B.
Dec. 5	Clear	99	0	0	++++‡	++++	++	++++
			1½ hrs.	1½	++	++++	+	++++
			4 hrs.	4	++	++++	+	++++
6	Clear	100	1 day	10	+	+++	−	++++
7	Partly cloudy	100						
8	Clear	100						
9	Clear	100	4 days	40	−	−	−	+
17			12 days	120	−	−	−	−

Relative humidity varied from 17 to 62 per cent; temperature from 45° to 76°F.

* From the U. S. Weather Bureau, Los Angeles, California.

† Sunrise to sunset.

‡ Amount of growth after 8 weeks of culture: + = 1 to 4 colonies; ++ = 5 to 20 colonies; +++ = 21 to 60 colonies; ++++ = 61 or more colonies; − = no growth; c = contamination.

TABLE 2

Exposure to roomlight and dark of smears containing 0.005 mg. tubercle bacilli

Recovery by culture

Experiment started at 11:00 a.m.

DATE, 1937	WEATHER	SUNSHINE PER CENT OF POSSIBLE	TIME ELAPSED	HOURS OF DAY-LIGHT	DAYLIGHT		DARK	
					Water smear	Sputum smear	Water smear	Sputum smear
Mar. 11	Cloudy	35	0	0	++++	++++	++++	++++
			1 hr.	1	++++	++++	++++	++++
12	Rainy	14	24 hrs.	12	+++	++++	++++	++++
13	Partly cloudy	46	2 days	24	−	−	++++	++++
14	Cloudy	61	3 days		−	−	++++	++++
15	Cloudy	8	4 days		−	−	++++	++++
17			6 days		−	−	++++	++++
20			9 days		−	−	++++	++
Apr. 20			40 days		−	−	−	−

During light exposure period, relative humidity varied from 35 to 94 per cent; temperature, from 52° to 78°F.

Mean relative humidity at 4:30 a.m. and noon: March, 73 and 47 per cent; April, 73 and 44 per cent.

Mean maximum and minimum temperatures: March, 67° and 50°; April, 72° and 53°F.

was negative at fifty-six and one-half hours (thirty-six and one-half hours of daylight) and thereafter while the next nearest animal inoculation, done at four days, was also negative. In the dark, culture and animal were both positive at fifty-five days, and culture was negative at seventy-five days, but no further animal inoculation had been done. Tubercle bacilli lived longer in sputum than in water smears: fifty-one and one-half (thirty-one and one-half

TABLE 3

Exposure of smears containing 0.5 mg. tubercle bacilli to roomlight and dark
Recovery by culture and guinea pig inoculation
Experiment begun at 10:00 a.m.

DATE, 1937	CLOUDINESS	SUNSHINE PER CENT OF POSSIBLE	TIME ELAPSED	HOURS OF DAYLIGHT	DAYLIGHT			
					Water smear		Sputum smear	
					Culture	Guinea pig*	Culture	Guinea pig*
July 20	5/10	63	0 hrs.	0	++++		++++	
			4 hrs.	4	++++		++++	
			7 hrs.	7	++++		++++	
21	4/10	68	23 hrs.	13	−		++++	
			27 hrs.	17	−		++++	
			31 hrs.	21	++++		++++	
22	5/10	64	51½ hrs.	31½	−	−	+++	++
			56½ hrs.	36½	−		−	
23	5/10	49	76 hrs.	44	−		−	
24	1/10	88	4 days	56	−	−	−	−
					DARK			
29			9 days		++++		++	++++
Aug. 12			23 days		+++		+++	
20			31 days		++		+++	
30			41 days		+	++	−	+
Sept. 13			55 days		−	−	+	++
Oct. 3			75 days		−		−	

During light exposure period relative humidity varied from 42 to 94 per cent; temperature from 61° to 89°F.

Mean relative humidity at 4:30 a.m. and noon: July, 88 and 53 per cent; August, 90 and 54 per cent; September, 79 and 49 per cent.

Mean maximum and minimum temperatures: July, 80° and 62°; August, 81° and 62°; September, 82° and 63°F.

* Amount of visceral tuberculosis: + = minimal at 2 months; ++ = minimal at 1 month; +++ = moderate at 1 month; ++++ = extensive at 1 month; − = none.

hours of actual light) as compared with thirty-one hours (twenty-one hours of actual light) in daylight; fifty-five as compared with forty-one days in the dark.

The following winter, sputum smears containing 0.5 mg. tubercle bacilli were exposed in roomlight, dark and in the electric refrigerator. Viability was tested by culture and animal inoculation. Except for the first day, the weather was clear during the period of light exposure. In the refrigerator smears were pro-

tected from light and kept at an average temperature of 45°F. and an average relative humidity of 67 per cent. As may be seen from table 4, the bacilli survived at least five days in roomlight (fifty hours of actual light), three and one-half months in the dark and six and one-half months in the refrigerator.

In the roomlight, cultures were positive after seventy-two hours or thirty-two hours of daylight, negative after ninety-two hours or thirty-six hours of

TABLE 4

Exposure in light, dark and refrigerator of sputum smears containing 0.5 mg. tubercle bacilli
Recovery by culture and guinea pig inoculation
Experiment started at 11:45 a.m.

DATE, 1938	CLOUDINESS	SUNSHINE PER CENT OF POSSIBLE	TIME ELAPSED	HOURS OF DAYLIGHT	DAYLIGHT		REFRIGERATOR	
					Culture	Guinea pig	Culture	Guinea pig
Jan. 19	7/10	51	0	0	++++			
21	1/10	100	46 hrs.	18	+++			
			52 hrs.	24	c	++++		
22	0	100	72 hrs.	30	++++	++++		
23	1/10	100	92 hrs.	36	−	+++		
			4 days	40	−	−		
24	1/10	100	5 days	50	−	++		
					DARK			
Feb. 12			24 days		++++	++++		
19			31 days		++++	++++		
28			40 days		+++	++++		
Mar. 17			57 days		+	+++	++++	
26			66 days		+	+++		
Apr. 9			80 days		−	+++	++++	++++
May 2			103 days		−	+++	++++	+++
June 25			158 days		−	−	++++	+++
Aug. 6			200 days		−	−	++++	+
Mar. 18, 1939			424 days				−	−

During light exposure period, relative humidity varied from 13 to 87 per cent; temperature from 49° to 75°F.

Mean relative humidity at 4:30 a.m. and noon: January, 54 and 37 per cent; February, 71 and 52 per cent; March, 71 and 46 per cent; April, 74 and 50 per cent; May, 81 and 52 per cent; June, 87 and 61 per cent.

Mean maximum and minimum temperatures: January, 70° and 52°; February, 64° and 49°; March, 65° and 50°; April, 70° and 53°; May, 72° and 55°; June, 73° and 58°.

In the refrigerator, the average temperature was 45°F. and the average relative humidity 67 per cent.

daylight. Guinea pigs were positive at ninety-two hours, negative at four days, but positive again at five days. The limit of viability was not definitely established, but negative cultures and the diminishing amount of tuberculosis in the guinea pigs suggest it was closely approached.

In the dark, cultures were positive at sixty-six days, not at eighty; animals were positive at one hundred three, not at one hundred fifty-eight days. In the

refrigerator, both cultures and animals were positive at six and one-half months and both negative at fourteen months.

When the results of the several experiments are compared it is seen that tubercle bacilli were recoverable more readily and after longer periods when the dose deposited was larger. When the dose was 0.000,05 to 0.005 mg. they were recoverable by culture after only four hours to one day in the light and nine days in the dark; but with a dose of 0.05 to 0.5 mg. they were culturable after two to three days in the light and fifty-five to sixty-six days in the dark.

In general the bacilli lived longer in smears made from sputum than in those made from water suspensions. Thus, in experiment 1, the maximum proven viability was four days for the former and one for the latter. In experiment 2 there was no difference, but in experiment 3 survival in the light was almost one day and in the dark fourteen days longer for sputum than for water smears.

As a test for viability, animal inoculation was superior to culture. Although in experiment 3 there was no apparent difference, in experiment 4 viable tubercle bacilli were demonstrable by animal two days longer in the light and thirty-seven days longer in the dark than by culture.

Tubercle bacilli lived longer in the winter than in the spring or summer: one, four and five days as compared with one and two days in the light; one hundred three as compared with nine and fifty-five days in the dark. However, it must be pointed out, the viability in winter darkness as shown by culture alone was between sixty-six and eighty days, not certainly greater than that of between fifty-five and seventy-five days in summer darkness.

Coincidentally with the increased viability of tubercle bacilli, the temperatures in the winter months were generally lower. During the daylight exposure periods, the temperature was between 45° and 76°F. in December; 49° and 75° in January; 52° and 78° in March; 61° and 89° in July. During the dark exposure periods, mean monthly maximum and minimum temperatures were for January, February and March, of experiment 4, 70° and 52°, 64° and 49°, 65° and 50°; for March and April of experiment 2, 67° and 50°, 72° and 53°; for July, August and September of experiment 3, 80° and 62°, 81° and 62°, 82° and 63°F.

The relative humidity fluctuated widely throughout all the experiments with readings varying from 7 to 99 and mean monthly values from 37 to 90 per cent. Differences did not seem sufficient nor consistent enough to account for changes in viability. The longer life of tubercle bacilli in the dryer periods of experiments 1 and 4 is more reasonably attributable to dosage and time of year. The average relative humidity of 67 per cent in the refrigerator was not notably different from the mean values outside, but the variations were much less extreme.

Cloudiness had no demonstrable effect on daylight viability. Survival of one and two days in the cloudy weather of experiments 2 and 3 was even less than that of four and five days in the clear weather of experiments 1 and 4. However, it must be remembered that the cloudiness in these experiments was never complete and there was always some sunshine.

DISCUSSION

The marked effect of dosage on the apparent survival of tubercle bacilli is perhaps attributable to limitations in the methods of recovery in that a positive result may require the presence of a number of viable microörganisms. Thus as the dosage increases, the number of bacilli surviving a given exposure would be expected to increase and culture or animal more likely to be positive. It also seems likely that bacilli in mass deposit are mutually protective against light and other adverse phenomena. A similar protective effect may account for the increased viability of tubercle bacilli in sputum smears. Sputum proteins may serve to block bactericidal radiations, to buffer extreme variations in pH or to mitigate the effects of atmospheric changes.

That the methods of recovery were reasonably good is suggested by the strongly positive results for all dosages in the early periods of exposure and the diminution in the amount of growth or animal tuberculosis as exposure increased.

Although survival was definitely favored by refrigerator temperatures, the greater viability of tubercle bacilli in winter as compared with spring and summer roomlight was probably not due so much to temperature or relative humidity as to the shorter winter days and their lower content of bactericidal radiations. The time between sunrise and sunset at Los Angeles is approximately ten hours in winter, twelve in spring, and fourteen in summer. As previously mentioned, noonday ultraviolet radiations are, in the winter, about one-half what they are in the spring and summer with the values for morning and afternoon still less in proportion. Thus the bactericidal light of a winter day is considerably less than half that of a spring or summer day.

In this connection it is well to point out that while light radiation at mid-day is maximal, that for the hours immediately after sunrise and before sunset is negligible in amount and therefore it is misleading to give the number of hours of daylight as a measure of the bactericidal action of the light.

As shown by Ives and Gill, the effect of partial cloudiness on sky radiation is difficult to predict and the failure to find a diminution in the lethal effect of daylight in our limited experience is not particularly significant. However, during completely cloudy weather, judging from tests made by these authors, we might well expect a measurable increase in the life of exposed tubercle bacilli. This should be particularly so during somber, heavily overcast periods.

Other possible factors in viability not considered above are the reaction of the sputum medium and the effect of antibodies and other bacteria contained therein; the chemical activity of the material on which the sputum is deposited; and the strain and age of the tubercle bacilli.

In applying our findings to the practical considerations of viability and, hence, infectivity of tubercle bacilli in the rooms of sanatorium patients, it must be remembered that the conditions of the experiments were extreme. The dosage employed in some cases was larger than what might be expected to be broadcast in a patient's room except with the most abandoned spitting. On the other hand, the north light to which the experimental preparations were ex-

posed may be considered minimal, less than that to which most parts of the rooms under consideration are exposed. Exceptions are, of course, places behind walls or furniture never reached by direct rays. Finally, in the experiments, almost *all* the material and microörganisms employed were either cultured or inoculated into guinea pigs, animals of inferior resistance. In practice, the human, an animal of relatively high resistance, breathes in at most but a small proportion of the bacilli that may be stirred up in the dust from the floor or furnishings or that may be suspended in the air in droplet nuclei.

All the evidence indicates that tubercle bacilli live a very short time in rooms well supplied with unfiltered daylight. In the dosages in which they are apt to be spread by trained patients of a well run institution, they probably do not survive in infectious quantities more than a few hours. In absolute darkness they may live several months. In partial darkness or subdued light, an intermediate viability would be expected. Where the light entering the rooms must pass through glass, the shorter ultraviolet rays will be filtered out and the bactericidal effect of the light largely nullified. Viable tubercle bacilli would be expected to survive relatively long periods in dark corners, in poorly lighted rooms and in rooms with glass-covered windows unless removed by other agents.

At high altitudes the sterilizing action of daytime roomlight should be even more potent. In northern latitudes, during the spring and summer when ultraviolet radiations are strong and windows are wide open, it should be comparable to that at Los Angeles. In the winter, on the other hand, when the days are shorter and bactericidal radiations are much less than in the South, when cold weather requires closed windows and when cloudiness and smokiness tend to be maximal, the situation is quite different. The effectiveness of roomlight is probably very small. Unless removed or killed by other measures, tubercle bacilli broadcast in patients' rooms may be expected to remain viable and infectious for relatively long periods, perhaps weeks and even months. Furthermore, deposit and survival of the bacilli would be cumulative with a progressive increase in their number from day to day. Under such circumstances the daily use of artificial ultraviolet rays with proper protection of the patient might well be considered as a substitute for sky radiation.

SUMMARY

1. Dried tubercle bacilli survived unfiltered north roomlight from four hours to five days under varying conditions. They were nonviable, according to the methods of recovery used, at one to twelve days, with the time not established in one case.

2. Viability in the dark was from less than forty days to between three and one-half and five months.

3. Viability in the refrigerator was between six and one-half and fourteen months.

4. Tubercle bacilli were more readily recoverable and after longer periods of exposure when the dose deposited was larger. Only with tremendous dosage were the bacilli recoverable after more than one day of exposure to room light.

5. They lived longer in smears made from sputum than from water suspensions.

6. They lived longer in the winter than in the spring and summer.

7. Variations in relative humidity and periods of partial cloudiness had no demonstrable effect on viability.

8. It seems probable that unfiltered daytime roomlight can play a very important rôle in preventing cross-infections and in protecting the employees of tuberculosis sanatoria and rest homes.

SUMARIO

1. Bacilos tuberculosos secos sobrevivieron por espacio de cuatro a cinco días la luz del norte sin filtrar en un aposento, en condiciones variables. Sin embargo, cesó su viabilidad al cabo de uno a doce días, lo cual varió según los métodos utilizados para descubrir los bacilos, mientras que en un caso no se estableció el período de tiempo.

2. La viabilidad a oscuras varió de menos de cuarenta días a entre tres y medio y cinco meses.

3. La viabilidad en el refrigerador varió de seis y medio a catorce meses.

4. Los bacilos fueron más fáciles de descubrir y al cabo de un período más prolongado de exposición, cuando la dosis depositada fué mayor, pero hubo que usar dosis tremendas para poder descubrir el bacilo al cabo de más de un día de exposición a la luz del cuarto.

5. Los bacilos vivieron más tiempo en frotes preparados del esputo que de suspensiones acuosas.

6. Vivieron más tiempo en invierno que en la primavera y verano.

7. Las variaciones en la humedad relativa y en los períodos de nublazón parcial no ejercieron efecto observable sobre la viabilidad.

8. Parece probable que la luz solar diurna sin filtrar pueda ejercer un papel muy importante en la prevención de las infecciones cruzadas y en la protección de los empleados de los sanatorios y las casas de reposo para tuberculosos.

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BLOOD SERUM CALCIUM IN NEGROES WITH TUBERCULOSIS[1,2]

HAROLD D. WEST AND NELSON C. JEFFERSON

Recently the blood serum clacium of 309 normal Negroes was investigated (1). The subjects studied were taken from widely separated geographical locations and represented various economic levels in the population. Three hundred and eighty-five determinations of blood serum calcium of 309 individuals gave values which varied from 9.03 to 11.86 mg. per 100 cc. with a mean of 10.39 mg. per 100 cc. It was concluded that blood serum calcium in the Negro is of the same order of magnitude as that of other groups of the population.

In view of the high incidence of tuberculosis and the scarcity of data on serum calcium in this condition in Negroes it was thought that it would be of interest to determine the level of this blood component in a series of these patients.

PROCEDURE

The determinations were carried out as was previously outlined (1). Blood was obtained from 7 patients at the George W. Hubbard Hospital and 28 patients at the Davidson County Tuberculosis Hospital.[3] There were 13 female and 22 male adults in the series. All of these subjects were hospital patients confined to bed.

RESULTS

The values of the serum calcium varied from 7.40 to 11.25 mg. per 100 cc. with a mean of 9.90 mg. per 100 cc. The most frequent values varied from 9.40 to 9.65 mg. per 100 cc. In 68 per cent of these cases values for calcium were below 9.99 mg. per 100 cc. Our findings in this study indicate that the average level of blood serum calcium is somewhat lowered in tuberculosis. The average level established by us for normal Negroes is 10.39 mg. per 100 cc. (1). A similar value, 10.30 mg. per 100 cc., is given as the normal average by Schmidt and Greenberg (2), while some adhere to the value 10.50 mg. per 100 cc. (3).

Studies in other laboratories have led to the same general conclusion. Halverson, Mohler and Bergeim (4) using a different method (5) and a milk diet in a series of 30 cases found maximum variations of 8.4 to 11.0 mg. per 100 cc. with averages slightly below normal in different groups except in improved cases. Matz (6) using the Kramer-Tisdall procedure found low average values of 9.22 mg. per 100 cc. in chronic pulmonary tuberculosis complicated by kidney disease

[1] From the Department of Biochemistry, Meharry Medical College, Nashville, Tennessee.

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[3] Thanks are due to Dr. R. D. Crowe and Dr. F. H. Aley for coöperation in obtaining these blood samples.

and 9.25 mg. per 100 cc. in chronic pulmonary tuberculosis with and without haemorrhage. Brockbank (7) also employing the Kramer-Tisdall procedure found serum calcium values, on the average, slightly lower in cases of advanced pulmonary tuberculosis than in normal subjects. It was stated by this author (7) however that values were slightly higher than the normal average in cases of pulmonary tuberculosis which had healed or were healing.

Harrell (8), in a study of 23 Negro patients diagnosed as having pulmonary tuberculosis, found an average value of 9.2 mg. per 100 cc. Six of these patients who died while the investigation was being made had an average calcium of 9.1 mg. per 100 cc. This author, however, has suggested as an average normal for blood serum calcium in Negroes 10.93 mg. per 100 cc. This would mean that in his study patients with tuberculosis showed a drop in serum calcium of 1.73 mg. per 100 cc. in the first group and 1.83 mg. per 100 cc. in the second group. Such differences between healthy individuals and patients with tuberculosis have no counterpart in the literature available to us. Indeed while the average values of serum calcium in tuberculosis obtained by us and the authors cited are definitely below the average for normals, the differences are generally of the order of not more than 0.2 to 0.4 mg. per 100 cc.

In searching about for an explanation of these slightly lowered average[4] values one possibility seems to deserve some comment. Eichelberger and McCluskey (9) studied total serum protein in 109 patients with tuberculosis. Total serum protein was found to be above 8 per cent in 55 and above 10 per cent in 3 subjects. The values varied from 6.005 to 11.135 per cent. There was an increase in globulin with a decrease in albumin in the majority of cases, the total protein remaining normal or slightly increased. Peters and Eiserson (10) have shown that in 100 cc. of serum containing 7 gm. of protein, 3.9 mg. of calcium is normally present as the proteinate. This represents the non-diffusible calcium of the blood serum and is in part dependent on the albumin/globulin ratio, since the anion concentration of the former is 50 per cent greater than that of the latter (11). It seems probable therefore that the low average values seen for calcium in tuberculosis may be due in part at least to the disturbed albumin/globulin ratio. Further investigation of the relation of blood serum protein to the calcium level in Negro patients is comtemplated.

CONCLUSIONS

1. In a series of 35 Negro patients with tuberculosis, blood serum calcium varied from 7.40 to 11.25 mg. per 100 cc. with a mean of 9.90 mg. per 100 cc.

2. These values are similar to those obtained by other authors who also found average values for calcium in tuberculosis slightly lower than the average normal value.

3. This lowered average value for blood serum calcium in tuberculosis is discussed in relation to the blood serum proteins.

[4] It is to be emphasized that *average* values rather than *individual* values are significant.

CONCLUSIONES

1. En una serie de 35 tuberculosos de raza negra, el calcio hemosérico varió de 7.40 a 11.25 mg. por 100 cc., promediando 9.90 mg. por 100 cc.

2. Estas cifras son semejantes a las obtenidas por otros autores, quienes también observaron que, en la tuberculosis, los promedios de calcio son levemente inferiores a los normales.

3. En este trabajo relaciónase esta disminución media del calcio hemosérico en la tuberculosis con los valores de las proteínas hemoséricas.

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RESULTS OF THORACOPLASTY[1]

A SYMPOSIUM PRESENTED AT THE TWENTY-FOURTH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THORACIC SURGERY, TORONTO, CANADA, JUNE 9, 1941

Surgery in Pulmonary Tuberculosis

RALPH ADAMS AND PAUL DUFAULT

A thirteen-year period of surgical therapy for pulmonary tubereulosis at one sanatorium is reviewed and the statistical results are reported. The material embraces 241 patients treated by thoracoplasty and 19 treated by extrapleural pneumothorax.

The important factors which have raised the rate of sputum conversion to 81 per cent in all sanatorium patients and 65.2 per cent following thoracoplasty and given an all-inclusive death rate of 15.7 per cent are analyzed. The discussion includes preoperative preparation, the use of ether as the anaesthetic agent, the type and technique of operation, the influence of apicolysis upon percentage and speed of conversion, postoperative care and complications, the reasons for failure and the causes of death in 260 consecutive cases.

Thoracoplasty

Late Results

GEORGE F. SKINNER, LACHLAN MACPHERSON AND IRENE ALLEN

The authors report 226 cases of thoracoplasty done between 1924 and 1940, more than half the total number having been operated upon since 1935.

Tables showing follow-ups at different periods with comparative figures are included.

Results with more extensive but more selective types of surgery as done in recent years are compared with those operated on five, ten and fifteen years ago.

The satisfactory cases are classified as apparently cured or improved. In

[1] The complete papers have been published in the Journal of Thoracic Surgery, October, 1941. The abstracts and summaries presented here are published by courtesy of the Editor of the Journal of Thoracic Surgery, Dr. Evarts A. Graham, and by courtesy of the publisher, The C. V. Mosby Company. The coöperation of the authors of these papers is gratefully acknowledged. [Ed.]

the former, cavities must be closed, sputum must be negative for tubercle bacilli and patients must be working. The improved patients are sputum-negative but either not sufficient time has elapsed to place them in the better group or some condition other than pulmonary tuberculosis has prevented them from working. All others are considered unsatisfactory or dead, there being only one case not traced.

The 226 cases are divided into three series. The first 50, done between 1924 and 1932, with resection of small segments of eleven ribs and averaging over ten years since operation, show 58 per cent good results (apparently cured and improved) with an early death rate of 12 per cent and 16 per cent late deaths from tuberculosis; 10 per cent died of causes other than tuberculosis and 4 per cent were still living but unsatisfactory.

The second series of 50 cases, with total removal of the upper ribs and a more selective collapse, showed over 65 per cent good results five to eight years after operation and an early death rate of 4 per cent. There were 18 per cent late deaths from tuberculosis and 10 per cent were unsatisfactory.

In the third series consisting of 126 cases done since 1936 and including 90 thoracoplasties combined with apicolysis, there were 80 per cent good results and an early death rate of 3.2 per cent.

The figures for the three series at a comparable early period after completion were: apparently cured and improved, 66 per cent, 76 per cent and 80 per cent respectively.

Attention is drawn to a decline in the immediate good results three to five years after completion, while after this period figures remain more or less stationary. The late deaths from tuberculosis and the unsatisfactory cases were practically all in the poor risk group or those complicated by empyema.

The 4 deaths in the last series are discussed and it is pointed out that the addition of apicolysis did not increase the operative risk; results were better and complications less, when compared with the whole series.

This trend toward removing fewer ribs has been further augmented during the last year by Leahy's suggestion of inserting the scapula inside the sixth rib. This tendency toward a selective collapse may be carried too far, but with equally good results the appearance of the chest does count as well as saving of vital capacity.

The disadvantage in the apicolysis procedure is the dropping of the apical cavities to a less collapsible position in the hilar region. This is probably a real danger if an extreme relaxation is done routinely, but this danger would seem to be eliminated if the pneumonolysis is mostly in the region of the anterior mediastinum and the paravertebral gutter, leaving the lung attached at the very apex or allowing the apex to drop only a few inches. Relaxation in all directions, rather than extreme dropping of the apex, is the aim.

Analysis of 100 Consecutive Cases of Thoracoplasty with No Operative Mortality

RICHARD H. DIEFFENBACH AND ANTHONY D. CRECCA

These 100 consecutive cases of thoracoplasty with no operative mortality were operated upon during the period 1936–1938 and the patients to date have been followed from three to five years. There were 221 operations on these 100 patients.

The following is a summary of the number of stages and the results in relation to negative sputum.

100 cases: A total of 221 operations

15 cases: One stage only	12 negative sputum
65 cases: Two stages	43 negative sputum
18 cases: Three stages	14 negative sputum
22 cases: With revision operation	14 negative sputum

Summary of the results in relation to concurrent and previous collapse therapy follows:

Thoracoplasty results

With contralateral pneumothorax
41 cases: 23 negative; 5 died; 13 still positive sputum
With previous pneumothorax sputum
57 cases: 40 negative; 8 died; 9 still positive sputum
With no previous pneumothorax
31 cases: 27 negative; 1 died; 8 still positive sputum
With 2nd operation or revision
22 cases: 14 negative; 1 died; 7 still positive sputum

In 8 cases the presence of tuberculous empyema was the reason for thoracoplasty. The thoracoplasty was followed by a Schede operation. In this group 7 patients had *empyema necessitatis*. All 8 had bronchopleural fistula. Three patients represented standovers from the old Sauerbruch thoracoplasty and a complete secondary operation had to be performed in each case.

The following summarizes the results as related to the existing disease at the time of operation.

Pathology

With contralateral caseous pneumonic lesion
38 cases: 21 negative; 7 died; 10 still positive sputum
With contralateral exudative productive lesion
14 cases: 10 negative; 2 died; 2 still positive sputum
With contralateral proliferative lesion
30 cases: 23 negative; 1 died; 6 still positive sputum
With previous pleural effusion
31 cases: 22 negative; 4 died; 4 still positive sputum

No vascular accidents occurred in this group.

Horner's syndrome occurred in 4 cases. This condition, we feel, is due to trauma of the sympathetic chain during mobilization of the lung. It has persisted with slight improvement in all cases.

There was one brachial plexus injury with parasthesia along the ulnar nerve; this subsequently disappeared.

Pleural tears happened in 4 cases. The complications following this were combated by postoperative deflation of the resulting pneumothorax and attempt to suture the tear with intercostal muscle and fascia.

In this group there are 50 males and 50 females (91 whites, 8 Negroes and one of the yellow race). The age groups are given in the following tabulation. Seventy-one cases are arrested with negative sputum and closed cavities; the patients are working or able to work. Sixteen patients still have positive sputum. Thirteen died from progression of disease.

Age Group	*Number of Patients*
14–20	9
21–30	47
31–40	30
41–50	14

Analysis of 104 Cases of Thoracoplasty

GEORGE G. FINNEY

Analysis of 104 cases of thoracoplasty for pulmonary tuberculosis, covering a period from April, 1932 to December, 1940, is presented. This is a consecutive series operated upon by Dr. Robert T. Miller and the author. The present status of the patients is given as reported by the physicians of the various sanatoria where convalescence took place following surgery. Follow-up has been obtained in nearly 100 per cent of the cases.

Particular consideration is given not only to the operative and ultimate mortality, the types of cases and number of operations, but also to the incidence of infection, since no special precautions were taken at operation other than scrupulously careful surgical technique. Type of operation done is described and also the importance of the position used on the operating table is stressed, with special reference to a small axillary pillow used to aid free respiratory movements.

The necessity for good anaesthesia is brought out, cyclopropane gas having been found very satisfactory.

The benefit of routine blood transfusion, started during the operation and continued until the patient is conscious in order to avoid the usual postoperative drop in blood pressure, is stressed.

Results of Thoracoplasty

H. MELTZER

A series of 181 cases of thoracoplasty operated on over the five-year period 1935–1940 is presented. The total is made up of one minimal, 31 moderately advanced and 149 far advanced cases, including 25 with empyemata complicating their pulmonary disease. One hundred and thirty-six of the far advanced cases had bilateral disease, and 30 of these had contralateral collapse. The contralateral collapse consisted of 20 pneumothoraces, 7 apicolyses combined with paraffin packs, 2 phrenic nerve evulsions and one bilateral thoracoplasty.

The 181 cases are further classified as: acute, 12 cases; subacute, 30 cases; chronic, 139 cases. The chronic cases are again divided into "good chronics," 72 cases; "bad chronics," 42 cases and chronics with empyema, 25 cases; this latter subgroup is made up of 17 pure tuberculous empyemata and 8 with mixed infection. Results in each group and subgroup are analyzed.

Ninety-two cases had thoracoplasty done on the right side, 89 on the left; 92 were males, 89 were females; the average age of males was 32.3 years, of females 29.9 years.

The multiple-stage posterior operation of Alexander was employed in all cases; 98 had anterior collapse supplementing the posterior stages; 12 had supplementary extrafascial apicolysis; 18 had scapulectomy in lieu of additional rib removal; the 8 mixed infection empyema cases required additional Schede-type revision.

Local anaesthesia was used exclusively in the 560 stages required for the 181 cases. One-half of one per cent novocaine solution with 2 minims of epinephrine 1:1000 added to each ounce was found most satisfactory. In one instance only were flushing, dizziness, rapid pulse and dyspnoea due to the anaesthetic noted and then not in prohibitive degree. In earlier operations 750 cc. of solution were used; in more recent operations 300 to 450 cc. were found adequate. Local anaesthesia has advantages over general anaesthesia: (*1*) the necessity of gentleness in handling tissues, (*2*) greatly reduced bleeding due to the action of epinephrine, (*3*) the opportunity for greater care in controlling bleeding, and (*4*) uninterrupted presence of the cough reflex; *1*, *2* and *3* minimize shock; *4* minimizes the danger of sputum blockage which might lead to atelectasis and/or spread of disease. Local anaesthesia is considered to have been an important factor in attaining the favorable results presented.

Seven-rib thoracoplasties averaged 140 cm. in length of ribs removed; this indicates the completeness of rib-removal employed and completeness of removal is also considered to have been an important factor in attaining favorable results.

Accidents attributable to operation included: 7 minor degrees of shock; 8 minor pleural tears that healed without misadventure; 6 cases of paradoxical respiration with one death; 8 instances of wound infection with one proving fatal; one case of respiratory failure with fatal outcome; 3 cases of moderate atelectasis with good recovery in each. Thus there was an early operative death rate of

3, or 1.6 per cent. Six cases had extension of disease following operation and of these 5, or 2.7 per cent, ultimately died; 7 other deaths from nontuberculous causes occurred remotely after operation, giving a total of 15, or 8.2 per cent, dead from all causes at the end of the five-year period.

One hundred and forty-three cases (79 per cent) had been nonbacillary for at least six months postoperatively on examination by sputum specimen, gastric contents and culture; 115 cases had been discharged to their homes and of these, at the end of the five-year period, 5 were dead from nontuberculous causes; 14 had had reactivation and were readmitted; 3 were classified as still active but not readmitted; 13 were quiescent; 20 were apparently arrested; 56 were arrested and 4 were apparently cured. Fifty-eight were working or able to work at least part time.

Analysis with regard to various factors gives the following results:

(*1*) Contralateral collapse with thoracoplasty is well tolerated and gives favorable results.

(*2*) Best results are obtained in the twenty-one to thirty year old group but middle-age is not a contraindication in well selected cases.

(*3*) Most favorable results are obtained in cases where disease has been present for four months to four years; cases with disease of ten years' standing show a marked decline in good results; cases with acute disease of less than four months' standing show the poorest results of all but, considering that these were classed as hopeless without operation, the results obtained merit further trial of thoracoplasty in the acute rapidly progressive type of case.

(*4*) Amount of disease plays a very important part in results; although the far advanced bilateral group shows 73.5 per cent nonbacillary, yet all the recorded deaths occurred in this group.

(*5*) Type and duration of preceding pneumothorax has little influence on results. Length of hospitalization and ultimate results seem better in those without previous pneumothorax.

(*6*) Extent of cavitation bears a direct relation to results; the greater the cavitation the worse the results.

(*7*) There are 166, or 91.8 per cent, living patients in the entire group and, of these, 143, or 86.1 per cent, are bacilli free.

Thoracoplasty in Bilateral Pulmonary Tuberculosis

ARTHUR M. VINEBERG, DOUGLAS ACKMAN AND MICHAEL ARONOVITCH

Fifty cases of bilateral pulmonary tuberculosis which had had unilateral thoracoplasty were reviewed and analyzed in an effort to discover why certain of them did well while others did not. Cases with well healed disease on the contralateral side were not included.

The contralateral side at the time of operation was classified in each case as retrogressing, quiescent or progressing, with or without cavity. This classification was based mostly on serial X-ray evidence over variable periods of time prior to operation.

Most favorable results were obtained in those cases which showed actively retrogressing disease even if the retrogression had been going on for only a short period of time. The so-called quiescent cases did not do quite as well. Those cases with progressive disease on the contralateral side gave poor results.

Results in Ninety Consecutive Thoracoplasties

ARTHUR H. AUFSES

The results of thoracoplasties for pulmonary tuberculosis upon 90 consecutive patients, from January 1, 1935 to July 1, 1940, are analyzed. All patients had positive sputum and visible cavitation prior to operation. Some were complicated by undrained tuberculous empyema. Eighty per cent of the patients were between the ages of twenty and forty years and a high percentage had long-standing disease.

The contralateral lung was considered inactive at the time of operation, but approximately 30 per cent had X-ray evidence of bilateral tuberculosis. Other measures rather than thoracoplasty are used in patients presenting active lesions in both lungs.

The classical upper selective thoracoplasty with complete resection of the first three ribs was used in practically all cases. One hundred and ninety-two operations were performed. Thirteen patients had one-stage procedures; 57 had two stages; 15 had three stages and 5 had four stages. In 37 patients a Semb extrafascial apicolysis was performed in addition to the rib resection.

The follow-up is from one to six years' duration and every case has been followed to date. There are 71 per cent arrested; 18 per cent not arrested; 7 per cent postoperative deaths and 4 per cent late deaths. The classification "arrested" conforms to the standards set by the National Tuberculosis Association.

Of special interest is the rehabilitation of the arrested cases. Of 43 patients operated upon before January 1, 1939, and discharged as arrested, 41 are working full time or doing their housework. This high percentage of rehabilitated patients is credited in part to the duration of postoperative sanatorium care and later graded hourly increases in work under medical supervision.

The 6 postoperative deaths were due to pneumonia, transfusion reaction, phlegmonous infection of the wound, pheochromocytoma of the adrenal and contralateral pulmonary atelectasis.

The reasons for failure were attributed to a long standing hard fibrotic pulmonary lesion in 6 patients and an abnormally long delay between the first and second stages in 5 patients.

The relation of the status on discharge to the present status shows that of those patients discharged as arrested only 4 turned positive later. On the other hand, 6 of those discharged with positive sputum are now arrested. This is in marked contrast to the results obtained by supplementary operations, such as, anterior costectomies and posterior revisions, the results of which were far from gratifying.

COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS[1,2]

Comparative Value of Different Procedures

L. W. THOMPSON AND ROBERT M. JANES

There has been a great deal of discussion whether artificial pneumothorax and other forms of collapse therapy actually accomplish the two main objectives in modern sanatorium treatment, namely, (*1*) the reduction of the treatment period, (*2*) the production of permanent cures.

It is proposed to present herewith some statistics, together with some observations, which seem to indicate that a proper selection of cases for the different forms of collapse therapy is an important factor in attaining the objectives above mentioned.

MORTALITY WITHOUT COLLAPSE

In 1933 Barnes (1) published a report on the prognosis of non-cavernous phthisis in 314 cases not given collapse; the average duration of treatment was 10.6 months and the patients were followed for a period of one to fourteen years. The death rate was: minimal, 15 per cent; moderately advanced, 31 per cent; far advanced, 66 per cent.

At the end of three years, 40 per cent of positive-sputum cases were dead and 15 per cent of negative-sputum cases; of those under twenty years of age forty-four died within three years.

The presence of cavities makes the prognosis much worse. McMahon and Kerper (2) in 1933 published their findings on 296 cavity cases and found that spontaneous healing occurred in 40 per cent of cavities under 2 cm. in diameter, 20 per cent of 3 cm. in diameter, 13 per cent of 4 cm. in diameter and 6 per cent of those over 4 cm. in diameter. Spontaneous healing of cavities occurred in only 17 per cent of patients under twenty-five years of age.

Simpson (3) in 1935 published the results of a follow up of 1,601 cases with X-ray evidence of cavity and found that 60 per cent were dead at the end of five years. It is to be noted that the majority of these cases had cavities 2 cm. or less in diameter. The fact that the cavities which Simpson studied were diagnosed by X-ray must be emphasized for, generally speaking, only 25 per cent of cavities exhibit cavernous breathing and 10 per cent of cavity cases show no abnormal physical signs whatever (Bendove (4)).

ARTIFICIAL PNEUMOTHORAX

Clinicians can cite pneumothorax cases who have done well and an equal number who have not. It has been our impression for some time that most

[1] From the Department of Thoracic Surgery, Toronto Hospital for Consumptives, Weston, Canada. The authors wish to thank Dr. M. J. McHugh, Medical Superintendent of this hospital, for the privilege of publishing this report.

[2] Read before the meeting of the Canadian Tuberculosis Association, Toronto, Canada, June, 1941.

of the unfavorable reputation that pneumothorax has acquired was due to the old custom of using it almost exclusively on advanced cases. In these cases pleural adhesions frequently prevented an efficient collapse of the diseased area.

These cases instead of getting selective collapse, got a contraselective collapse. There is no more certain method of producing tuberculous empyema than putting tension on tuberculous lung contained in adhesions. It should be emphasized that the tissue in adhesions is frequently under considerable tension in the presence of quite negative intrapleural pressure. It is our belief that a pneumothorax which cannot easily be made efficient by cutting the adhesions or supplementary phreniclasia should be abandoned at once and another form of collapse used. This belief is substantiated amply by a 1940 publication of Jennings, Mattill and Nemic (5) in a review of twenty years' experience with unilateral pneumothorax on 1,027 patients.

Results of pneumothorax—Jennings, Mattill and Nemic

	PER CENT WORKING	PER CENT ALIVE BUT NOT WORKING	PER CENT DEAD
Satisfactory pneumothorax	81.9	13.4	4.2
Partly satisfactory pneumothorax	56.8	12.6	30.6
Unsatisfactory pneumothorax	23.1	10.2	66.2
No free space, therefore no pneumothorax	38.8	18.4	42.8

Jennings, Mattill and Nemic give the following illuminating figures on the latter two groups of cases, who did not have a satisfactory pneumothorax: no further collapse—249 cases, 74.6 per cent dead at the end of three years; further collapse—346 cases, 28 per cent dead at the end of three years.

THORACOPLASTY

When pneumothorax is unsuccessful the usual operation of choice is thoracoplasty. Four hundred twenty-four thoracoplasty operations were done on 162 cases from 1933 to 1938 inclusive. The number of case-years is sufficient to give a reliable indication of the prognosis after thoracoplasty. The results are given in the following tabulation.

Results on 162 thoracoplasty cases at the Toronto Hospital completed two to eight years

	NUMBER	PER CENT
Working full time	38	60.5
Working part time	60	
Improved	27	16.7
Unimproved or worse	7	4.3
Early deaths	7	4.3
Late deaths	11	6.8
Not traced	12	7.4

*Effect of thoracoplasty on sputum**

Sputum positive before thoracoplasty		128
Died with positive sputum from operative side	5	
Half of untraced group	6	21
Living with positive sputum from operative side	10	
Sputum conversion		83.5 per cent

* Definition of negative sputum: (*a*) patient reports no sputum; (*b*) 8 negative concentrated smears.

Gastric lavages and cultures were not used on this group of patients.

Thoracoplasty cases grouped according to condition before operation

	FAVOURABLE CASES (62 PER CENT OF TOTAL)	UNFAVOURABLE CASES (38 PER CENT OF TOTAL)
	per cent	*per cent*
Working full time	28.2	13.0
Working part time	47.4	21.0
Improved	16.0	27.5
Worse	4.2	12.3
Early deaths	0.8	12.3
Late deaths	0.8	11.0
Untraced	2.5	2.6

Discussion of Thoracoplasty Results

Four of the 7 early deaths were due to pulmonary embolism. Five of the 11 late deaths were caused by nontuberculous disease. The operative mortality in emypema cases was 25 per cent, compared to 3 per cent for the pulmonary cases. All but one of the empyema cases that died were secondarily infected before operation.

This experience has led us to treat all tuberculous empyemata by aspiration and irrigation with 1:3300 Azochloramid; 2 to 15 cc. of 1:500 Azochloramid are instilled at the end of the irrigation. This routine cures many tuberculous empyemata and prevents secondary infection in the others but it is quite time consuming.

Caseous type disease: Thirty-five per cent of the parenchymal cases showed no evidence of fibrosis and were classified as exudative-caseous type disease. The 6 late deaths from pulmonary tuberculosis occurred in this group; 8 of the 10 living cases with positive sputum from the operative side fall into this classification; 4 of these cases had a temporarily negative sputum. A very complete collapse of the diseased area must be produced in this type if subsequent liquefaction and evacuation of the caseous material, with the production of new cavities, is to be prevented. The other 4 non-fibrotic cases who have persistently positive sputum had thin-walled cavities surrounded by comparatively healthy lung. In our experience these thin-walled cavities surrounded by healthy lung are easier to collapse by extrapleural pneumonolysis than by thoracoplasty.

Indications for anterior stage thoracoplasty: It is easier to remove the anterior part of the first and second ribs and their cartilages from the back, when a

large curved incision is used for the upper posterior stage, than to remove them through an anterior incision. Unfortunately this has one distinct disadvantage, namely that the pectoralis minor is not divided when the ribs are completely removed from the posterior approach. In 5 of the above mentioned non-fibrotic cases with persisting positive sputum the pull of the pectoralis minor on the anterior part of the second, third and fourth ribs seemed to be the factor which prevented an efficient collapse. In 3 others, failure to realize the necessity to remove the transverse processes resulted in an inefficient collapse. When dealing with non-fibrotic upper lobe cavities, especially thin-walled ones, it is our present practice to include an anterior stage with division of the pectoralis minor in the plan of collapse.

The use of the Semb apicolysis: A limited apicolysis after the manner described by Semb is indicated in the treatment of thin-walled cavities near the apex surrounded by a good deal of healthy lung. A single stage thoracoplasty with apicolysis is useful for collapsing small apical cavities while in the process of active fibrotic contraction. Otherwise the Semb procedure would seem to be contraindicated because the cavity drops necessitating removal of more ribs.

Effect of disease in the contralateral lung: Forty-eight cases, or 28 per cent, had minimal or more disease in the opposite lung, by X-ray appearance not judged to be healed before thoracoplasty. Four of these died of this disease from one to five years after the operation. In 10 cases the disease in the opposite lung is worse producing positive sputum in 8 of them. If the disease in the better lung does not seem to be healed it is apparent that a pneumothorax should be started before thoracoplasty is done on the worse side. Fifteen cases with pneumothorax on the opposite lung have had thoracoplasties to June 1, 1941. Only one has died.

Effect of age and duration of disease on mortality: Seven cases, 30 per cent, of the age group above forty years (24 cases) have died whereas only seven per cent in the age group twenty to forty years. Patients who have had tuberculosis for more than five years and are more than forty years of age are particularly bad risks.

Right side compared to left side: There was no appreciable difference in mortality or conversion of sputum between right and left sided cases. Patients who have had a right thoracoplasty have, on the average, more dyspnoea.

Vital capacity: One-third of the cases had a vital capacity below 50 per cent of their normal average. The mortality in this group was twice as high as the group with vital capacity more than 50 per cent of their normal average.

EXTRAPLEURAL PNEUMONOLYSIS

Eleven patients had extrapleural pneumonolysis at the Toronto Hospital for Consumptives, Weston, prior to July, 1938. The results in these cases were disappointing because unsuitable cases were operated on and the operative technique and after-care left much to be desired. Therefore, a preliminary re-

port of the cases done since that period will give a better picture of the results that may be obtained.

Extrapleural Pneumothoraces, July, 1938 to December, 1940

Total patients: 30 (2 had bilateral operations)
Right side: 14 operations
Left side: 18 operations

Patients were divided into predominantly exudative type, chronic caseous type and acute caseous pneumonic type.

Chronic caseous type—22 cases: Average duration of disease was 3.3 years. Westergren sedimentation rate varied from 10 to 45. Mean sedimentation rate was 22. Conversion of sputum was obtained in 18 of 19 cases who had positive sputum before operation (94.7 per cent). Closure of cavity according to x-ray evidence occurred in 17 out of 19 cases. Tuberculous empyema developed in 5 cases; 4 of these have been cured by aspiration and irrigation. Obliterative pleuritis developed in 3 cases but the sputum remains negative in 2 of these. One male, age fourteen, died one month after operation from peritonitis subsequent to rupture of a tuberculous ulcer; one female, thirty-two years of age, died ten months after her operation from bilateral renal tuberculosis.

Exudative type—4 cases: Average duration of disease was 5.5 months. Westergren sedimentation rate varied from 27 to 60. Conversion of sputum occurred in all 4. Closure of cavity, as seen by X-ray, occurred in all 4. Tuberculous empyema developed in 2 cases; both were cured. Both empyema cases had moderate tuberculous enteritis, now much improved by calcium and diet. None died.

Acute caseous pneumonic type—4 cases: Average duration of symptoms was 5.5 months. Westergren sedimentation rate varied from 70 to 77. Cavity closed in only one case, who later developed a bronchopleural fistula and empyema. All 4 cases died from pulmonary tuberculosis one month to one year

Preliminary report of 32 extrapleural pneumothoraces on 30 patients including 2 bilaterals

	CHRONIC CASEOUS	EXUDATIVE	PNEUMONIC PHTHISIS
Number of operations	22	4	4
Average duration of disease	3.3 years	5.5 months	5.5 months
Erythrocyte sedimentation rate (W)	10–45 mm. (mean 22 mm.)	27–60 mm.	70–77 mm.
Closure of cavity according to X-ray	86 per cent	100 per cent	25 per cent
Sputum converted	94.7 per cent	100 per cent	0
Tuberculous empyema			
Developed	5 cases	2 cases	1
Cured	4 cases	2 cases	0
Obliterative pleuritis	3 cases	0	0
Deaths	2 cases (nonpulmonary)	0	4

after operation. All had advanced tuberculous enteritis. Three cases did not develop tuberculous empyema until they became moribund.

Discussion of Results of Extrapleural Pneumonolysis

The most frequent complication following extrapleural pneumonolysis is tuberculous empyema in the extrapleural space. The more difficult the stripping of the pleura the greater the possibility of subsequent empyema. Apparently stretching the diseased lung tends to produce tuberculous empyema as in intrapleural pneumothoraces. The stripping should therefore be carried well down on the chest wall and mediastinum. The cases which developed obliterative pleuritis were those in which sufficient stripping had not been carried out. To obtain a good result the lung should be freed for at least two interspaces below the lower level of the pulmonary cavity, shown in the preoperative X-ray film. It is possible, then, to collapse the lung slowly by a gradually increasing positive pressure, reaching a maximum of 20 cm. of water at the end of one month. The air pressures used must be governed by frequent fluoroscopic examinations. After the first week it is better to keep the space dry and give nitrogen refills to those cases who continue to form fluid. Even clear fluid should be aspirated and Azochloramid instilled. Care should be taken not to injure the underlying lung with the needle. Patients with symptoms of tuberculous enteritis seemed more prone to the development of empyema.

One case developed staphylococcus empyema ten days after the operation. It was cured by daily Dettol irrigations and instillations. To-day such a patient would be given sulphathiazole.

CONCLUSIONS

1. Collapse therapy offers a much better prognosis for pulmonary tuberculosis than bed-rest alone. This is especially true for patients with cavities.

2. A satisfactory artificial pneumothorax is the treatment of choice but an inefficient pneumothorax is likely to be a liability rather than an asset.

3. Where an efficient pneumothorax cannot be established it should be abandoned at once and another form of collapse instituted.

4. If pneumothorax cannot be used thoracoplasty is the next safest and most widely applicable form of collapse therapy.

5. If a good anterior collapse from thoracoplasty is desired the pectoralis minor muscle should be divided.

6. Extrapleural pneumothorax is the treatment of choice for acute or chronic thin-walled cavities of 3 cm. in diameter or less which are surrounded by comparatively healthy lung. This is especially true of cavities in the apex of the lower lobes and lingual process of the upper lobes.

7. Extrapleural pneumothorax is the treatment of choice in adolescents with minimal lesions that progress or are stationary under bed-rest alone.

8. Extrapleural pneumothorax is often the treatment of choice where thoracoplasty is difficult or dangerous on account of bilateral disease, advanced non-

pulmonary tuberculosis or nontuberculous disease. Extrapleural pneumothorax is of little or no value in acute caseous pneumonic phthisis.

9. Cavities larger than 3 cm. in diameter which are surrounded by caseous disease are best treated by thoracoplasty.

CONCLUSIONES

1. La colapsoterapia ofrece un pronóstico mucho mejor que el encamamiento exclusivo en la tuberculosis pulmonar, sobre todo si existen cavernas.

2. Un neumotórax artificial satisfactorio constituye el tratamiento de elección, pero si es ineficaz resultará probablemente ser un gravamen más bien que una ayuda.

3. Cuando no puede establecerse un neumotórax eficaz, debe abandonarse en el acto e instituirse el colapso en otra forma.

4. Si no puede utilizarse el neumotórax, la toracoplastia constituye la forma de colapsoterapia que le sigue en seguridad y aplicación más general.

5. Si se desea obtener un buen colapso anterior con la toracoplastia, hay que seccionar el pectoral menor.

6. El neumotórax extrapleural constituye el tratamiento de elección en las cavernas, ya agudas o crónicas, de paredes delgadas, que miden 3 cm de diámetro o menos, y que se hallan rodeadas de tejido pulmonar comparativamente sano, rezando esto en particular con las del vértice de los lóbulos inferiores y el proceso lingual de los superiores.

7. El neumotórax extrapleural constituye el tratamiento de elección en los adolescentes si tienen lesiones mínimas que se estacionan o continúan evolucionando con el encamamiento solo.

8. El neumotórax extrapleural constituye a menudo el tratamiento de elección cuando la toracoplastia resulta difícil o peligrosa debido a la existencia de afección bilateral, tuberculosis extrapulmonar avanzada o afección no tuberculosa. En cambio, posee muy poco o ningún valor en la tisis neumónica caseosa aguda.

9. En las cavernas de más de 3 cm de diámetro, rodeadas de tejido caseoso, el mejor tratamiento es la toracoplastia.

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PNEUMOTHORAX VERSUS APICAL THORACOPLASTY

SIDNEY J. SHIPMAN[1]

The problem of pulmonary tuberculosis may be considered either from the public health standpoint or from the standpoint of the sick individual. If we adopt the former viewpoint, the elimination of positive sputum is the *sine qua non* of all our efforts and justifies the most extreme measures, provided only that the sputum of sick patients be made negative. The latter viewpoint often requires the reverse attitude, tolerating a small amount of positive sputum for the sake of the individual's life, work and enjoyment. This latter viewpoint would rely upon education if necessary for the protection of the community. Which viewpoint is the more to be desired I do not know. Certainly there is no doubt about it when we, personally, are concerned. Yet all of us know clinicians in charge of sanatoria who adopt the former attitude, using collapse therapy to the extent of rendering their patients chronic invalids in order to get rid of the last cubic centimeter of positive sputum. Probably from all standpoints a middle course is most desirable, that is, a course which utilizes to the fullest extent the advantages of collapse therapy, always stopping short of irreparable harm to the individual's respiratory function, and at the same time employing education and moral suasion wherever they may be indicated.

This attitude requires a rather close critique of collapse therapy. Pneumothorax, being simple and therefore most commonly employed, is usually advocated as the first step in any collapse therapy program. However, a critical attitude would suggest that one inquire whether there are any disadvantages to pneumothorax as it is now employed. And it should be added at once that agreement should be obtained for the concept that compressing the lung and ridding the patient of positive sputum should be only half the treatment; the other half should be considered the reëxpansion of the lung and the restoration of the thoracic contents to something approaching normal. Unless pneumothorax does this, then all should agree that there are other methods that do it better.

Pinner and Rubin (1) say "The risk of serious complications in pneumothorax is real and should not be minimized. . . . Prolonged collapse causes fibrosis and pleural thickening, which may prevent complete reëxpansion of the lung and cause impairment of the respiratory reserve. . . . An important contraindication is a disease process which is amenable to spontaneous healing on bedrest and a dietetic-hygienic regimen. It is of almost equal importance to know when not to give pneumothorax as to know when to give it."

With these statements I most heartily agree. In these days of the "dynamic treatment" of pulmonary tuberculosis it is refreshing to discover such eminent authorities advocating bed-rest, which cured countless people before neophytes learned how easy it was to push needles through the chest wall. However, this is not germane to the present discussion. The point is that Pinner and

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Rubin believe that pneumothorax, simple as it is, has certain serious disadvantages.

Turning to the surgeons, no less an authority than Dr. E. J. O'Brien of Detroit (2) stresses the disadvantages of pneumothorax. "Pneumothorax, both intrapleural and extrapleural, is fine going down, and you get beautiful and immediate results, with negative sputum, but there is a long, hard, rough road ahead before the patient's lung is reëxpanded and he is rehabilitated and back in the community. How much more beautiful is thoracoplasty."

There seems to be no doubt that Doctor O'Brien prefers thoracoplasty.

The fact is that almost all clinicians who have had extensive experience with artificial pneumothorax have been disturbed by distressing late results. The sequence of events is usually this: the patient has a lesion limited to one apex with a positive sputum. He may or may not have a small cavity. The lung is collapsed by pneumothorax and a good collapse obtained, save for an adhesion or two which do not appear to interfere with the collapse. The sputum becomes negative. In an attempt to lengthen the refill interval to save the patient expense or arrange for a vacation or possibly to stretch the adhesions, more air than usual is given, the intrapleural pressure is somewhat elevated, and when next observed fluid is found in the pleural cavity. This persists or gradually rises. The pleura visibly thickens. Unless the lung is allowed at once to reëxpand (and sometimes even then) the lung rapidly becomes encased in a cuirass of thick pleura, the diaphragm is elevated and becomes adherent to the chest wall, and a great deal of function of the involved lung is irrevocably lost (figures 1 and 2).

If this sequence of events were rare, it might be neglected. But it is distressingly common. How common it is, probably depends upon the care with which pneumothorax is given. In the hands of careful operators who select their cases well, watch them closely, giving air frequently and in small amounts, using a selective collapse if possible and intrapleural pneumonolysis only with the greatest caution, it is at a minimum. When carelessly given with large amounts of air at long intervals and great variations in intrapleural pressure, one can almost predict that the result, regarding reëxpansion and restoration of function, will be poor.

There remains the question of how much function may be impaired. So far entirely adequate studies covering the point are lacking. One of the most fruitful attempts to investigate the problem is that of Cournand and Richards (3), who investigated "pulmonary function in pulmonary tuberculosis under various forms of collapse therapy." In 11 cases with reëxpanded lungs following the completion of pneumothorax treatment the main differences were "(*1*) a decrease in total capacity with a significant increase in the proportion of residual air; (*2*) a significantly smaller maximum breathing capacity." These changes were somewhat less than those observed in 31 thoracoplasty cases, but it should be noted that the thoracoplasties were five to ten rib operations. In the attempt to investigate this problem in a crude way it has been the practice at the Tuberculosis Division of the San Francisco Hospital to get vital capacity

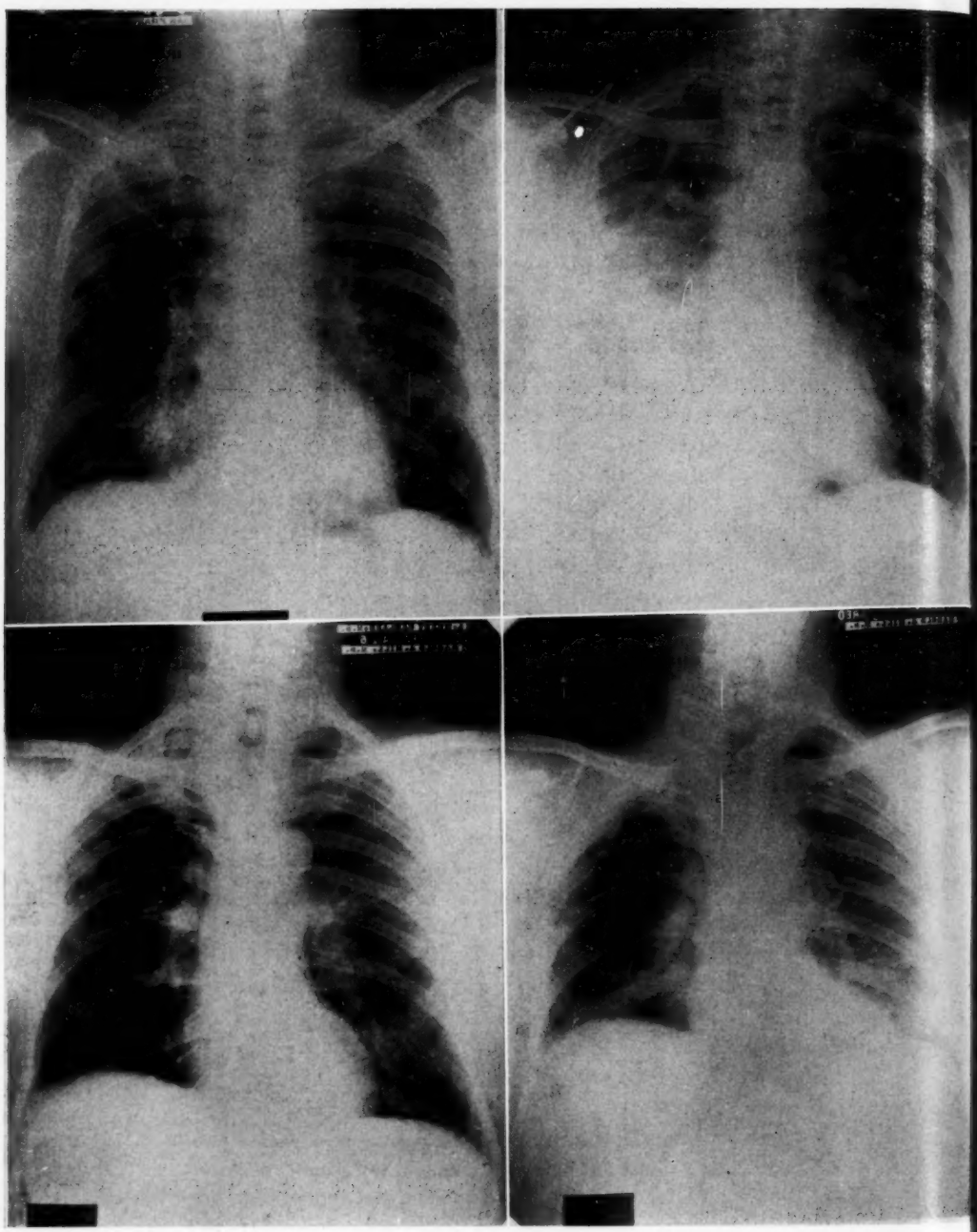

FIG. 1. (Upper left.) A., age thirty, before pneumothorax. Cavity behind first rib and in right first interspace (May 18, 1940).

FIG. 2. (Upper right.) A., after pneumothorax. Cavity closed and sputum negative but function of lung seriously impaired May 6, 1941. Total period of invalidism one year.

FIG. 3. (Lower left.) R., age fifty-six, before thoracoplasty. Small cavity behind right first rib (January 3, 1938).

FIG. 4. (Lower right.) R., after thoracoplasty. Cavity closed and sputum negative (March 10, 1939). Total period of invalidism three months.

studies before and after pneumothorax on every patient, but the time necessary to complete treatment and allow reëxpansion makes it impossible to draw definite conclusions at this time.

An important factor is the function of the diaphragm. Best and Taylor (4) assert that 60 per cent of the total amount of air breathed during deep respiration is accounted for by the action of the diaphragm. Cournand and Richards (*loc. cit.*) state that phrenicectomy "appears regularly to disturb pulmonary function to a considerable extent." From clinical observation it is common knowledge that the action of the diaphragm is often impaired after reëxpansion of a previously collapsed lung and may be totally destroyed.

In view of these facts we are moved to remark with O'Brien "how much more beautiful is thoracoplasty;"—especially apical thoracoplasty. The removal of three ribs is often enough if thoracoplasties are used in early cases. There is no mortality and practically no complications. In our experience the loss of vital capacity in these cases has varied from 0 to 200 cc. (figures 3 and 4). If the removal of five ribs is necessary the loss will be little greater.

Appreciation of the above facts has led us to adopt the following procedure at the University of California Service of the San Francisco Hospital:

1: Use pneumothorax only after a period of bed-rest, unless urgent indication, such as hemorrhage, exists.
2: Give frequent small refills with low pressures.
3: Unless the pneumothorax is entirely satisfactory, or can rapidly be made so by the severance of small adhesions, abandon it at once.
4: If fluid forms during the course of pneumothorax treatment, cease refills until it has absorbed, or aspirate. If fluid persists, abandon the pneumothorax without delay.
5: Respect pneumothorax more than thoracoplasty.

By following these precepts we have had no case of empyema which developed following pneumothorax therapy in the past four years.

In conclusion I might say that a good apical thoracoplasty is better than a poor pneumothorax. Personally I dread the needle more than the knife.

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BRONCHOSCOPIC SUCTION[1]

An Aid in the Closure of Cavities in Pneumothorax Cases

HARRY MEYERSBURG, HARRY GRUBER AND CARL W. LUPO

Since the advent of bronchoscopy, medical literature abounds with unmistakable evidence supporting its ever widening field of usefulness. It is now generally conceded to be indispensable in the accurate diagnosis of lesions of the respiratory and upper digestive tracts.

Until a few years ago, pulmonary tuberculosis was held by most authorities to be an absolute contraindication to peroral endoscopy. Many thoracic specialists have since altered their attitude and not a few have taken a more courageous stand in respect to advising bronchoscopy in active pulmonary tuberculosis. As a result, considerable data are now available, nearly all of which have to do with corroborative and differential diagnosis, especially as regards endobronchial tuberculosis.

Therapeutically, the use of the bronchoscope has been shown to be effective in the treatment of bronchiectasis, certain forms of lung abscess, croup, asthma, atelectasis and many other nontuberculous inflammatory conditions, apparently with little untoward effect even on debilitated individuals. In pulmonary tuberculosis, while it is a relatively recent procedure, its routine application has not been generally accepted because no reasonable assurance of its therapeutic value has been demonstrated. It can, however, be said that the procedure is well tolerated by tuberculous patients when performed by experienced workers.

This paper purports to demonstrate the influence of bronchoscopic treatment on 3 patients who had pneumothorax for six to ten months, but their cavities were still open, and in whom other aids to closure of cavity—thoracoscopy with severance of adhesions, and/or phrenic crush—were attempted without success.

CASE REPORTS

Case 1: (Figure 1) E. F. male, white, age twenty-four, admitted September 28, 1938, acutely ill, sputum Gaffky VI, sedimentation rate 25. X-ray films taken October 1 and October 10, 1938 (figure 1A) showed rapid caseation with cavity formation. Pneumothorax was started October 21, 1938. Because of open cavity and persistently positive sputum, thoracoscopy was done on February 15, 1939 but no adhesions were found. Pneumothorax was continued without avail. In March, 1939 the lung was allowed to

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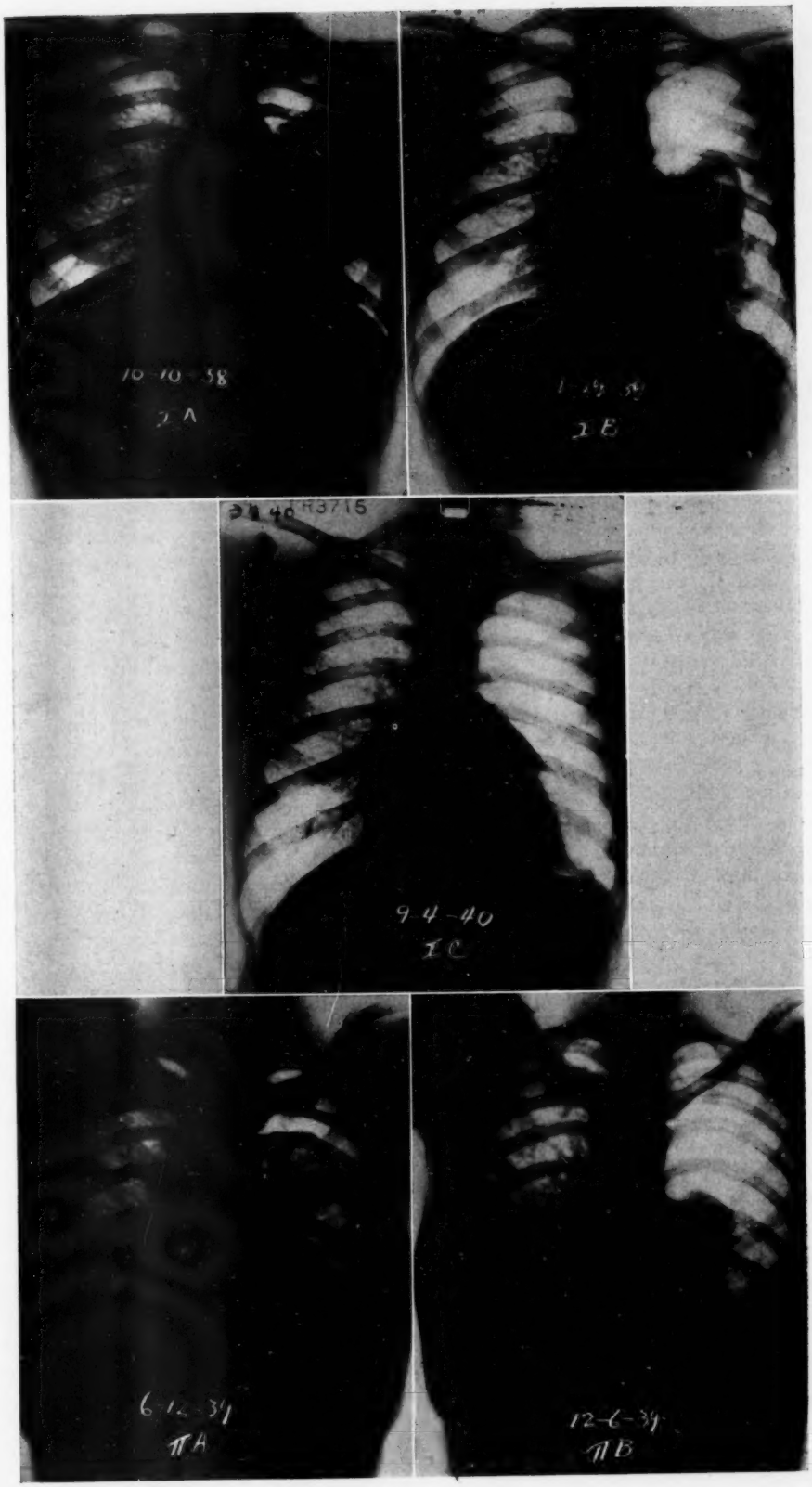
FIG. 1. A. (upper left) On admission. B. (upper right) Uncollapsed cavity, free pleural space. X-ray similar to time of bronchoscopic treatment. C. (center) X-ray similar to present status. This has been maintained since one month after suction therapy. Note improvement on opposite side.

FIG. 2. A. (lower left) X-ray day before bronchoscopic suction and after lung allowed to reëxpand to about 50 per cent. Pleural space is entirely free. B. (lower right) X-ray similar to present and status since eight weeks after aspiration.


10-10-38
1A
1B
9-4-40
1C
6-12-34
11A
12-6-34
11B

reëxpand to about 50 per cent and on April 7, 1939 (six months after institution of collapse therapy) bronchoscopy was done. No lesion was observed in the larynx or trachea; a small amount of mucopurulent material was removed from the left main bronchus. At the junction of the upper lobe bronchus there was oedema and congestion of the mucosa; a curved spring suction tip was introduced and, after overcoming a moderate resistance, was felt to enter a cavity from which retained secretion was aspirated. Four days later (April 11, 1939) there was X-ray evidence that the cavity was smaller. Pneumothorax was continued and increased amounts of air were given. One month after bronchoscopic suction, there was X-ray evidence of disappearance of the cavity with satisfactory collapse of the lung. Sputum which had been alternatingly positive and negative became persistently negative. Gastric lavage examinations following bronchoscopy were all negative for tubercle bacilli. Clinical condition rapidly improved. At present, patient is receiving his refills in the out-patient clinic and is working eight hours a day. Sputum and gastric lavages are still negative.

Case 2: (Figure 2) R. R., female, white, age twenty-six, admitted June 11, 1938, acutely ill, sedimentation rate 28, sputum Gaffky IV to X. Pneumothorax was begun on September 1, 1938. Phrenic crush was done January 25, 1939 without effect on cavities. Pneumonolysis was done March 15, 1939, six thin cord-like adhesions were present, all were severed. However, the cavity remained open, in spite of pneumothorax being pushed to the point of producing a mediastinal shift. The lung was then allowed to reëxpand to about 50 per cent prior to bronchoscopic suction (figure 2A). On June 13, 1939 (nine months after institution of pneumothorax) a bronchoscope was passed; the mucous membrane of the left main bronchus was thickened and granular in appearance; a curved spring suction tube was passed with moderate resistance; about three drams of bloody fluid were aspirated. Sputum, which had been persistently positive, became negative within one month and has remained negative. Examinations of gastric contents were now also negative. Cough and expectoration disappeared entirely in a short time. An X-ray film taken three months after bronchoscopic suction showed that the cavity was no longer visible. During these three months, the patient was fluoroscoped prior to each pneumothorax refill and the cavity showed diminution in size and then disappearance within eight weeks. Tomographic examination was done and these confirmed the absence of cavity. Condition of patient has remained good and prognosis is good, patient receiving refills in the out-patient clinic. All sputa to date are negative.

Case 3: P. W., white, male, age twenty-four, admitted April 1, 1939, sputum Gaffky IV to VIII. Pneumothorax was instituted June 6, 1939. Sputum became negative the following month and remained so. However, after six months of pneumothorax, the hilar cavity was still visible and had not responded to collapse therapy. Bronchoscopic suction was therefore done on December 1, 1939. A specimen of secretion from the left main bronchus was obtained. There was present the characteristic oedema at the mouth of the upper lobe bronchus; a large curved spring suction cannula was introduced encountering moderate resistance; the cavity was entered and suctioned out, yielding about two drams of bloody mucoid material. On examination of the smears, the one from the main bronchus was negative, while the secretion from the cavity proper was Gaffky III. An X-ray film taken two weeks after suction treatment showed a questionable annular shadow, and a later film, undeniable disappearance in five weeks. For one week following treatment the patient raised an average of 30 g. of sputum per day which was more than three times his previous daily average expectoration. After the

first week, his daily expectoration dropped to 2 to 6 g. daily. Patient's condition on discharge was good. All sputa since bronchoscopic suction have been negative. He is receiving refills from his private doctor.

DISCUSSION

Three cases of open cavity with pneumothorax are presented to show the influence of bronchoscopic suction. Two of the cases had received pneumothorax for six months and one for nine months prior to suction therapy. All 3 had thoracoscopic examination and, where present, adhesions were severed. All 3 cases, therefore, should have been ideal for collapse treatment by pneumothorax, but cavity still remained open. Within a relatively short period of time (four to eight weeks) following bronchoscopic suction, the 3 cases were converted from an unsatisfactory type of collapse to a therapeutically and anatomically satisfactory one. Clinical improvement was also noted, which consisted of diminished cough, reduction in the amount of sputum, slowing of the sedimentation rate and increase in weight.

We have found that the best time to perform this suction procedure is when the lung is not more than 50 per cent collapsed. This renders the upper lobe bronchi more easily accessible by altering their plane in relation to the lumen of the bronchoscope.

Our cases demonstrate cavities with bronchial obstruction, ball valve in type, proximal to the cavity in question. The cases all showed bronchial oedema and congestion and offered moderate resistance to the passage of the suction cannula. In one case there was a granular appearing bronchus, in the other 2 there was no evidence of endobronchial tuberculosis. From each case we were able to obtain secretion.

These were the only 3 cases seen in a two-years study, in which there was an open cavity in a completely free pleural space of at least six months' duration. Yet in each case, a good therapeutic result was obtained. This procedure was also attempted on 2 cases of poorly collapsed lungs in which the lobe with the cavity was adherent to the thoracic wall. However, it was not surprising to note no effect on the cavity in these 2 cases by the bronchoscopic aspiration.

In the cases herewith presented, there were tuberculous lesions in the opposite lung. Yet, as frequently happens, control of the more diseased side aided in the control of the opposite side.

The 3 patients are still receiving pneumothorax refills, all are sputum negative, and have had gastric lavages which have been likewise negative.

We realize, of course, that no definite conclusions can be deducted from the preceding case reports. They are presented with the expectation that they may stimulate others to investigate the value of bronchoscopic suction as a therapeutic procedure in selected cases of tuberculosis in which pneumothorax has not been entirely effective.

SUMMARY

Three patients with open cavity in spite of pneumothorax are presented in which bronchoscopic aspiration was performed. Pneumothorax had been given

for six to nine months prior to suction treatment and each case had a free pleural. Within four to eight weeks following the procedure, an unsatisfactory collapse was converted to a therapeutically and anatomically satisfactory one in each patient. The procedure is best performed when the lung is not more than 50 per cent collapsed. Clinical improvement rapidly followed closure of cavities.

SUMARIO

Descríbense tres casos de cavernas que permanecieron abiertas a pesar del establecimiento del neumotórax, en los cuales se ejecutó la aspiración broncoscópica. El neumotórax había sido aplicado de seis a nueve meses antes de la succión, y en todos los casos estaba despejado el espacio pleural. Al cabo de cuatro a ocho semanas de la aspiración, un colapso incompleto se convirtió terapéutica y anatómicamente en satisfactorio en todos los enfermos. El procedimiento resulta más fácil cuando el pulmón no presenta más de 50% de colapso. La mejoría clínica sobreviene rápidamente después de cerrarse las cavernas.

PARADOXICAL ABDOMINAL MOTION IN HEMIDIAPHRAGMATIC PARALYSIS[1]

A Test for Unilateral Phrenic Paralysis

WILLIAM J. HABEEB

The induction of diaphragmatic paralysis in the treatment of tuberculosis has increased interest in the function of the diaphragm and in the means of detecting the presence or absence of paralysis.

LITERATURE

Before the advent of roentgenography, percussion and auscultation were used more extensively than now to determine the motion of the diaphragm. Litten's test was described in 1892 but it failed to provide information in a large percentage of cases. Hoover (1, 2, 3, 4, 5) and Head (6, 7) in their clinical and experimental studies of the respiratory muscles in health and disease added much to our understanding of the function of the diaphragm. Hoover reported that the normally functioning diaphragm exerts a pull upon the lower ribs in a medial direction tending to restrict costal motion, while in hemidiaphragmatic paralysis an increased upward and outward excursion of the lower ribs occurs on the side of paralysis. Head recorded graphically the costal movements before and after unilateral phrenic paralysis and concluded that the ribs on the sound side move more rapidly during the first phase of inspiration while those on the side of paralysis move faster in the latter phase of inspiration. As evidence that there are difficulties in detecting diaphragmatic motion by physical signs alone, Lemon (8) as recently as 1928 stated that increased costal motion, homolaterally, is so inconstant as to be of no clinical value as a test for diaphragmatic paralysis.

In recent years fluoroscopy and the more accurate fluoroscopic signs of phrenic paralysis have relegated the physical signs to a position of secondary importance but not to entire obscurity.

Hoover and Head made observations on costal and diaphragmatic motion but they gave no especial attention to the motion of the abdomen. Their subjects used simple breathing. Since there is no perceptible variation in the motion of the abdomen on quiet breathing with or without hemidiaphragmatic paralysis, due to the small part played by the diaphragm in quiet breathing, it is understandable that the abdomen has been overlooked in seeking clues to the function of the diaphragm. Although Hitzenberger (10) made no mention of abdominal motion, his fluoroscopic observation of paradoxical motion of the diaphragm was made on sniffing.

Sniffing is a sudden inspiration primarily diaphragmatic in character; it exaggerates the motion of the normal and paradoxical motion of the paralyzed diaphragm. Likewise, it exaggerates the motion of the abdomen and under normal conditions produces a sudden, equal protrusion of both sides of the abdomen which is most marked in the two upper quadrants. When hemidiaphragmatic paralysis is present sniffing brings out a characteristic abdominal

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

motion which, as far as can be determined, has not been described previously.[2] The motion consists of a disparity in the degree of protrusion of the two sides of the abdomen. On the sound side the abdomen protrudes as usual on sniffing but on the paralyzed side a decrease in the degree of protrusion occurs, which may be termed paradoxical. For example, in left hemidiaphragmatic paralysis the abdominal protrusion is greater on the right than on the left side, while in right phrenic paralysis the protrusion is greater on the left than the right side of the abdomen. In a few thin patients, retraction of the upper abdomen on the side of paralysis has been observed.

The paradoxical abdominal motion on sniffing can be used as a simple, gross test for unilateral phrenic paralysis. It is not expected that its use will supersede but supplement the use of the fluoroscope in testing the motion of the diaphragm. Proper elicitation of the motion requires that the patient be supine and relaxed while sniffing. The patient should be instructed to take his time between sniffs but to make each sniff quickly. The examiner should stand at the patient's feet to determine the disparity in the upper abdominal protrusion.

The mechanism of the abdominal motion: Normally, the diaphragm descends on sniffing, decreasing the longitudinal diameter of the abdomen, raising the intraäbdominal pressure, compressing the abdominal viscera and producing an equal protrusion of both sides of the abdomen. With hemidiaphragmatic paralysis, the unparalyzed hemidiaphragm descends normally, on sniffing, while the paralyzed hemidiaphragm ascends into the thorax. The absence of abdominal protrusion on the side of paralysis depends on this paradoxical motion[3] of the paralyzed hemidiaphragm. The decrease or absence of protrusion has not been observed in the absence of the paradoxical motion of the diaphragm. Further, the greater the paradoxical motion of the paralyzed hemidiaphragm, the less the abdominal protrusion on the side of paralysis. In a few instances where the paradoxical motion of the diaphragm is quite marked there is actual retraction of the abdominal wall.

Results: One hundred patients were tested who did not have phrenic paralysis and no patient in this group showed the paradoxical abdominal motion seen with phrenic paralysis. One hundred patients with unilateral paralysis were tested and 84 of these showed paradoxical abdominal motion while 16 did not.

[2] Standard textbooks of neurology and physical diagnosis make brief mention of the physical signs of bilateral diaphragmatic paralysis in which one sign is recession of the abdomen on inspiration and bulging on expiration. No report has been found in which a distinction has been made between the abdominal motion in bilateral and unilateral diaphragmatic paralysis.

[3] Paradoxical diaphragmatic motion, on sniffing, is the result of decreased intrathoracic as well as increased intraäbdominal pressure. The paralyzed leaf ascends in response to the decreased intrathoracic and the increased intraäbdominal pressure. Paradoxical diaphragmatic motion may occur with partial paralysis or weakness. Hitzenberger (10) has reported paradoxical diaphragmatic motion in diaphragmatic weakness due to malignant, inflammatory, parasitic and degenerative diseases. Alexander (9) believes that immobility of the diaphragm is a more proper test of diaphragmatic paralysis than either elevation or paradoxical motion.

The presence or absence of phrenic paralysis was verified by fluoroscopic examination of all patients.

Variations in abdominal motion: The abdominal motion in hemidiaphragmatic paralysis varies in different patients. The disparity in the motion on the two sides of the abdomen may be greater in one patient than another. In some patients the difference in motion on the two sides is hardly perceptible. In testing patients the disparity in the motion on the two sides of the abdomen was graded on the basis of 1 to 4 in which 1 indicates the least and 4 the greatest disparity in motion observed. On that basis the greatest disparity has been observed in left hemidiaphragmatic paralysis in men. That is, the disparity was grade 4 in most male patients with left hemidiaphragmatic paralysis, while few male patients with right hemidiaphragmatic paralysis showed more than grade 3 disparity in motion. This can be explained by the anatomical differences in the two sides of the abdomen. Approximately five-sixths of the liver occupies the space beneath the right hemidiaphragm. The liver, being a solid viscus, serves better in transmitting the force of the contracting right hemidiaphragm than hollow viscera, such as the stomach and intestines which are compressible and tend to cushion the force of the left diaphragm when it descends.

Another variation has been noted which depends on the type of sniffing. Sniffing in most men is primarily diaphragmatic in character. For that reason men show more marked abdominal protrusion on sniffing than women, who have a more costal type of breathing and sniffing. Very few women show a grade 4 disparity in motion.

In a few particularly thin female patients the abdomen on the side of the paralysis has been seen to retract slightly on sniffing. Retraction of the abdomen on the side of paralysis suggests marked paradoxical motion of the paralyzed hemidiaphragm due to marked decrease in the intrathoracic pressure.

Negative tests with phrenic paralysis: As stated previously, the characteristic abdominal motion seen in unilateral phrenic paralysis has not been observed in the absence of paradoxical motion of the paralyzed hemidiaphragm. It is known that there is little chance for paradoxical motion with such conditions as extensive diaphragmatic adhesions, positive pressure pneumothorax, pleural effusion or extensive pulmonary consolidation. If one or more of these conditions is present, the abdominal as well as the fluoroscopic signs of phrenic paralysis may well be absent. Two patients have been observed who had extensive diaphragmatic adhesions and homolateral phrenic paralysis in whom the test was negative. Another patient who had an ineffective positive pressure pneumothorax on the right was given a homolateral phrenic crush and the lung was allowed to reëxpand. On the first few days following the phrenic crush the abdominal sniff test was negative because there was no paradoxical motion of the diaphragm due to the positive pressure, but as the air absorbed paradoxical motion became visible fluoroscopically and more marked as time passed. Concomitantly the abdominal test became positive and more markedly so, as the degree of paradoxical motion increased.

A few patients were tested who could not learn to sniff properly. Instead of sniffing they persisted in taking simple deep inspirations which, though quick, were not quick enough to be actual sniffs. These patients all showed retraction of the abdomen bilaterally, due to the marked thoracic excursion, irrespective of the presence or absence of phrenic paralysis.

Several patients who had thin, narrow chests with narrow subcostal angles showed so little abdominal motion on sniffing that it was impossible to determine the presence or absence of phrenic paralysis. The reason for this observation was not obvious.

SUMMARY

1. A simple physical test for hemidiaphragmatic paralysis is described.
2. The test consists of observing the degree of protrusion of the upper abdomen on sniffing, while the patient is supine.
3. Normally, on sniffing, an equal protrusion of both sides of the abdomen occurs which is most marked in the two upper quadrants.
4. In hemidiaphragmatic paralysis, a decrease or absence of upper abdominal protrusion occurs on the side of phrenic paralysis.

SUMARIO

1. Descríbese una sencilla prueba física para la parálisis hemidiafragmática.
2. La prueba consiste en observar el ángulo de protrusión de la porción superior del abdomen al resoplar, mientras el enfermo se encuentra en decúbito supino.
3. En estado normal, al resoplar obsérvase una protrusión igual de ambos lados del abdomen, que es más acentuada en los dos cuadrantes superiores (hipocondrios).
4. En la parálisis hemidiafragmática obsérvase disminución o falta de dicha proyección abdominal superior en el lado de la parálisis del frénico.

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VITAMIN K IN TUBERCULOSIS[1,2]

With Special Reference to Pulmonary Haemorrhage

SOL LEVY

The discovery of the so-called "Koagulationsvitamin" (vitamin K) by Dam and Schönheyder, Almquist and Stockstad in 1934–1935 followed the original observation of Dam that newly hatched chicks, maintained on a certain diet, suffered fatal haemorrhages, which could be prevented or cured when the chicks were fed alfalfa.

Subsequent investigations identified this haemorrhagic disease as a true deficiency disease and led to the opinion that haemorrhagic diseases in man were of similar nature. Not until the isolation and synthesis of vitamin K by Doisy, Karrer, Fieser and others was it possible to investigate its clinical use and value.

In one of the first publications on this subject, Quick in 1935 found that prothrombin, one of the four agents required for blood coagulation, was the important factor in cholaemic bleeding and that the liver plays the major rôle in the transformation of vitamin K to prothrombin.

Vitamin K, in its natural form, is fat-soluble and requires the presence of bile for its utilization. Following its absorption from the intestine it is carried to the liver where it is utilized, in a manner yet unknown, to form prothrombin. If the absorption of vitamin K is sufficiently reduced by the lack of bile, or if there is an insufficient supply of the vitamin in the diet, or if hepatic damage interferes with the synthesis of prothrombin, the blood concentration of the latter falls. When a sufficiently low level is reached, marked increase in the clotting time of the blood occurs and haemorrhage is likely to start at the slightest injury.

In 1938 Quick reported that the administration of vitamin K and bile was indicated in jaundiced patients in whom prothrombin deficiency was demonstrated. This work represents the basis for the use of vitamin K in the treatment of haemorrhagic diathesis due to obstructive jaundice.

At the same time Quick described a simple test for the quantitative determination of the blood prothrombin. This was followed by the two-stage titration method of Warner, Brinkhous and Smith, the micro-prothrombin method of Kato, and the "bed-side" method of Smith, Ziffren, Owen and Hoffman.

The quantitative estimation of blood prothrombin helped to limit the use of vitamin K to cases of hypoprothrombinaemia due to (*1*) diet deficient in vitamin K, (*2*) defective intestinal absorption or (*3*) exclusion of bile from the intestine. On the other hand, the administration of vitamin K has little if any benefit in the correction of hypoprothrombinaemia in the face of extensive liver damage.

With the rationale of vitamin-K therapy established, a voluminous literature has accumulated in the past three years with reports of excellent results in the use of this vitamin in certain haemorrhagic diseases of the newborn, obstructive jaundice (stone, stricture, pancreatic disease), biliary fistula, nontropical sprue, intestinal obstruction, ulcerative colitis and in the prophylaxis of postoperative bleeding in the jaundiced patient.

[1] From the Maryland Tuberculosis Sanatorium, Mount Wilson Branch, Mount Wilson, Maryland.

[2] Parke, Davis & Co. supplied the vitamin K preparation (Synkamin) used in this study.

Only one reference in the literature has been found dealing with vitamin K in tuberculosis. In a series of articles published in Boll. Soc. ital. biol. sper. (April, 1940) Scoz, Bergami and Castaldi reported the clinical value of vitamin K in tuberculosis and its effect in controlling haemoptysis. They determined the blood prothrombin concentration (Quick method) in patients with pulmonary tuberculosis and normal controls and concluded that neither the clinical form of tuberculosis nor the existence and frequency of haemoptysis seemed to have any definite influence on the blood prothrombin concentration. Although 30 per cent of the patients with tuberculosis had a definite hypoprothrombinaemia, a slightly larger percentage of normal controls showed a similar condition. It was observed that tuberculous patients treated with vitamin K showed an immediate though transitory rise of the blood prothrombin concentration. When blood prothrombin determinations were made on patients at the time of haemorrhage and found low, administration of vitamin K raised the blood prothrombin level and in some cases brought a cessation of the haemorrhage.

Scoz, Bergami and Castaldi admitted that their statistics were too scanty to draw any definite conclusions. On the other hand, the data obtained were complete enough to indicate that the administration of vitamin K (together with opiates) had definite value in the treatment of pulmonary bleeding.

The present study was undertaken to determine the relationship of vitamin K and tuberculosis with special reference to pulmonary haemorrhage.

MATERIAL AND METHODS

The material for this study consisted of 60 patients and 15 controls divided into the following five groups:

Group I (6 females, 9 males): History of long standing tuberculosis; extensive bilateral disease with cavitation; positive sputum; recurrent haemorrhages within past six months.
Group II (7 females, 8 males): Same history, same X-ray picture and same sputum status as in group I. Differed in that there was no haemorrhage within past six months.
Group III (7 females, 8 males): History of tuberculosis of at least six months' duration; X-ray lesions of infiltration (no cavities); negative sputum; no history of haemorrhage at any time during the illness.
Group IV (8 females, 7 males): History of longstanding tuberculosis; successful thoracoplasty of at least a year's duration; negative sputum; ambulatory.
Control Group (8 females, 7 males): Selected from professional and lay staff. No history of tuberculosis; no X-ray evidence of tuberculosis. All apparently well.

The following determinations were made in this study: the bleeding time (Duke), the coagulation time (capillary tube), prothrombin time (Smith "bedside," Quick) and the liver function test (hippuric-acid test, Quick).

To determine the bleeding time, a slight cut was made in the lobe of the ear and at half-minute intervals the blood was blotted with a piece of absorbent paper and the time recorded when bleeding ceased.

To determine the coagulation time, blood was obtained by venipuncture, at once transferred to a test tube and from there into a capillary tube about 0.5 mm. in diameter. Short sections of the tube were then carefully broken off at half-minute intervals. The time which elapsed between the transfer of the blood into the capillary tube and the

formation of threads of fibrin, which spanned the gap between the broken ends of the tube, was measured by means of a stop-watch and recorded as the coagulation time.

To determine the prothrombin time (Quick) 4.5 cc. of blood was obtained by venipuncture and immediately mixed with 0.5 cc. of a 1.34 per cent anhydrous sodium oxalate solution. The oxalated blood was centrifuged; 0.1 cc. of plasma was mixed with 0.1 cc. of thromboplastin solution (50 mg. in 1 cc. water) and the tube agitated in a water bath at 37.5 C. for about three minutes; 0.1 cc. of a 0.275 per cent anhydrous calcium chloride solution was quickly added to the mixture and the time elapsing between the addition of the calcium chloride solution and clot formation was measured in seconds by means of a stop-watch and recorded as the prothrombin time.

To determine the clotting power (Smith *et al.*) 0.1 cc. of a freshly prepared thromboplastin solution is put into each of two small test-tubes. To one tube is added, immediately after being drawn, 0.9 cc. of blood from the patient and into the other tube 0.9 cc. of blood from the control and the time noted. The test tubes were inverted once to mix the blood and the thromboplastin. Then the tubes were tilted every few seconds until the blood was seen to clot and the time noted to the nearest second. The clotting power was then calculated according to Smith's formula:

$$\frac{\text{Clotting time of normal blood}}{\text{Clotting time of patient's blood}} \times 100$$

The hippuric-acid test of liver function, as described by Quick, is based on the fact that hippuric acid, which results from the synthesis by the liver of benzoic and amino-

TABLE 1

Average bleeding time (Duke) in different groups

	GROUP I	GROUP II	GROUP III	GROUP IV	CONTROL
Average	4′ 15″	3′ 30″	3′	3′ 15″	2′
Highest	6′ 15″	5′	6′	5′	3′ 15″
Lowest	1′ 30″	3′ 15″	1′ 30″	1′ 30″	1′ 15″

acetic acids, is normally excreted in the urine at a nearly constant rate of 3 g. in four hours. To perform the test the patient is given a light breakfast of toast and coffee followed in one hour by 6 g. of sodium benzoate (dissolved in 30 cc. of water and flavored with a little oil of peppermint) in half a glass of water. Immediately after taking the drug the bladder is emptied and then the urine is collected hourly for four hours. Each specimen is measured, acidified with 1 cc. of concentrated hydrochloric acid and stirred vigorously until the hippuric acid precipitates. The precipitate is allowed to stand for one hour at room temperature, collected by filtration and dried in air. Each dry sample of hippuric acid is weighed to the second decimal place and by Quick's formula converted into benzoic acid values. Normally 3 g. of benzoic acid is excreted in four hours, with a normal variation from 2.55 to 3.30 g.; an excretion of less than this amount is indicative of impaired hepatic function.

RESULTS

The first study was the determination of the bleeding time (Duke). The average bleeding time in the different groups is presented in table 1, in which the highest and lowest values of each group are also given. Normal bleeding time with this test ranges between one and three minutes.

Although no unusually high values in either group were found, it is noteworthy that the highest values occurred in group I, patients with recent pulmonary haemorrhage. Furthermore, the average bleeding time in each of the four groups was at least 50 per cent higher than that of the control group.

The second study was the determination of the coagulation time. The results are given in table 2. Normal coagulation time, determined by this method, lies between two and six minutes.

These figures do not represent any abnormal values. An interesting observation, which, however, does not seem to have any further significance, is the fact that the range between the highest and lowest coagulation time in all four groups of patients was greater than that of the control group, where all the values lie between four and five minutes.

TABLE 2

Average coagulation time (capillary tube) in different groups

	GROUP I	GROUP II	GROUP III	GROUP IV	CONTROL
Average	4′ 15″	4′ 30″	5′	5′ 45″	4′ 15″
Highest	6′ 30″	5′	7′	8′	5′
Lowest	3′ 30″	3′	3′	3′ 30″	4′

TABLE 3

Average clotting power, in per cent, (Smith test) in different groups

	GROUP I	GROUP II	GROUP III	GROUP IV	CONTROL
Average	84.4	89.5	101.7	100.0	100.0
Highest	111.0	110.0	132.5	118.5	114.0
Lowest	61.0	75.0	76.5	84.0	90.0

The "bed-side" test (Smith *et al.*) was performed to determine the prothrombin time. In order to obtain the most accurate values, the prothrombin time in all groups was checked with the Quick test. It was found that the results of both tests corresponded almost 100 per cent. For reasons of simplicity and uniformity only the findings of the "bed-side" test will be used; and throughout the remainder of this paper the term "clotting power" will be used in place of prothrombin "time" or "level" or "concentration." The clotting power is calculated by Smith's formula, as given above, and it should be pointed out that a high clotting power indicates a low prothrombin time.

In table 3 are presented the average, highest and lowest clotting power values as obtained by the Smith test and confirmed by the Quick test. The normal clotting power, in per cent, is obviously 100; corresponding to between twenty-five and forty seconds.

According to Smith, clotting power values below 70 per cent definitely indicate a hypoprothrombinaemia, those between 70 per cent and 85 per cent indicate a mild degree of hypoprothrombinaemia, and those between 85 per cent and 100

per cent and over are normal. Applying these values to the results obtained it was found that in the four groups of patients

3 patients (5 per cent) had values below 70 per cent
16 patients (26.6 per cent) had values between 70 per cent and 85 per cent
22 patients (36.6 per cent) had values between 85 per cent and 99 per cent
19 patients (31.6 per cent) had values of 100 per cent and over

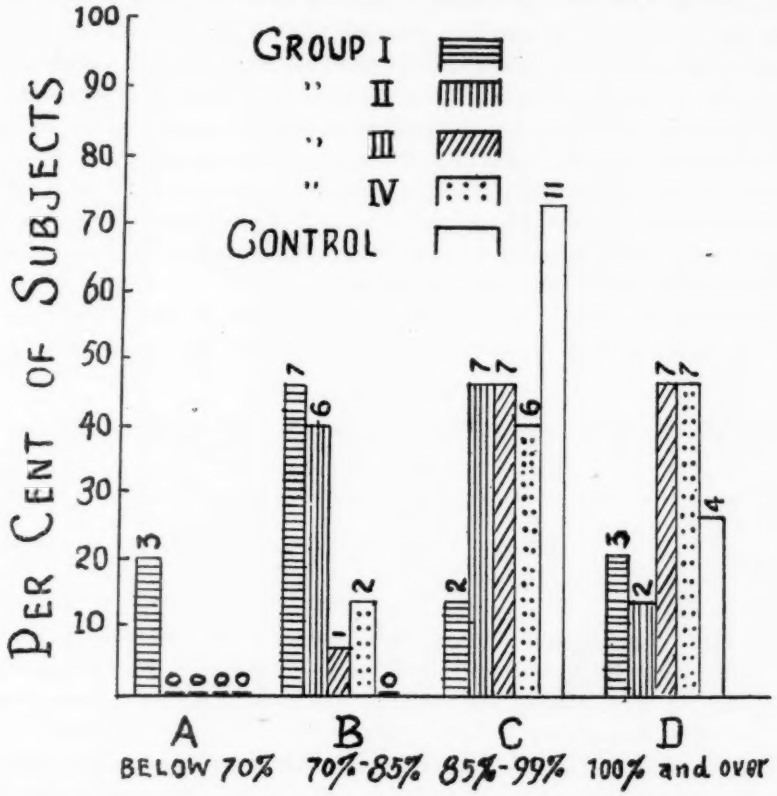

CHART 1. Relationship of each group to the different clotting power values

The table shows that about one-third of the patients with pulmonary tuberculosis reveal a more or less marked degree of hypoprothrombinaemia.

The results from the control group showed

None had values lower than 85 per cent
11 (73.3 per cent) had values between 85 per cent and 99 per cent
4 (26.6 per cent) had values of 100 per cent and over

When these values are compared with those of the patients with pulmonary tuberculosis, it is seen that the control group reveals no evidence of hypoprothrombinaemia, with the majority showing values between 85 per cent and 99 per cent.

Chart 1 contains four graphs, in which the relationship of the five groups to

the different clotting power values is demonstrated. Graph A shows the relation of each group to values below 70 per cent, graph B to values between 70 per cent and 85 per cent, graph C to those between 85 per cent and 99 per cent and graph D to those of 100 per cent and over. (The numbers on top of each square represent the number of patients.)

Examination of the chart shows that groups I and II appear chiefly in graphs A and B, showing that the low clotting power values are most marked in individuals with a history of long-standing tuberculosis. The majority of the other groups are represented in graphs C and D, showing normal clotting power.

The results of the hippuric-acid liver function test (Quick) are presented in table 4. Since the liver plays the dominant role in the transformation of vitamin K to prothrombin, this test was included as a routine procedure in the study. The figures in this table are given in percentages, where 100 per cent represents the excretion of 3 g. of benzoic acid in four hours. Variations of from 85 per cent to 110 per cent are considered normal, while values below this are definitely indicative of some disturbance of liver function.

The figures in the table clearly demonstrate that the groups of patients with histories of long-standing tuberculosis have a rather definite degree of liver

TABLE 4

Average values of liver function test, in per cent, (Quick) in different groups

	GROUP I	GROUP II	GROUP III	GROUP IV	CONTROL
Average	60.3	69.0	70.0	61.6	86.0
Highest	111.0	112.0	87.0	71.3	102.0
Lowest	27.0	42.0	43.0	47.0	75.0

damage. This liver damage may be secondary to myocarditis (toxic) or amyloidosis, both of which are not uncommon findings in chronic tuberculosis. There may be other factors producing the liver damage in these patients, but discussion of these pathological aspects is beyond the scope of this presentation.

Quick, in describing the test, considered values below 85 per cent as indicative of parenchymal liver damage. Experience with this test led to the necessity of distinguishing between different degrees of liver damage, so that values below 66.6 per cent (that is, the excretion of less than 2 g. of benzoic acid in four hours) are considered indicative of a more severe degree of liver damage, while values between 66.6 per cent and 85 per cent point to a slight degree of damage. Applying the results of the test to these newly established values, it is found that out of 60 patients with pulmonary tuberculosis

34 (56.6 per cent) had values below 66.6 per cent
18 (30 per cent) had values between 66.6 per cent and 85 per cent
8 (13.3 per cent) had values of 85 per cent and over

These figures show that more than four-fifths (86.6 per cent) of patients with pulmonary tuberculosis reveal a more or less marked degree of parenchymal liver damage.

The same values applied to the control group show:

None with values below 66.6 per cent
5 (33.3 per cent) with values between 66.6 per cent and 85 per cent
10 (66.6 per cent) with values of 85 per cent and over

This indicates a mild liver dysfunction in one-third of the normal controls.

The relationship of the five groups to the different liver function values is demonstrated in chart 2. Graph A shows the relation of each group to values below 66.6 per cent, graph B to values between 66.6 per cent and 85 per cent,

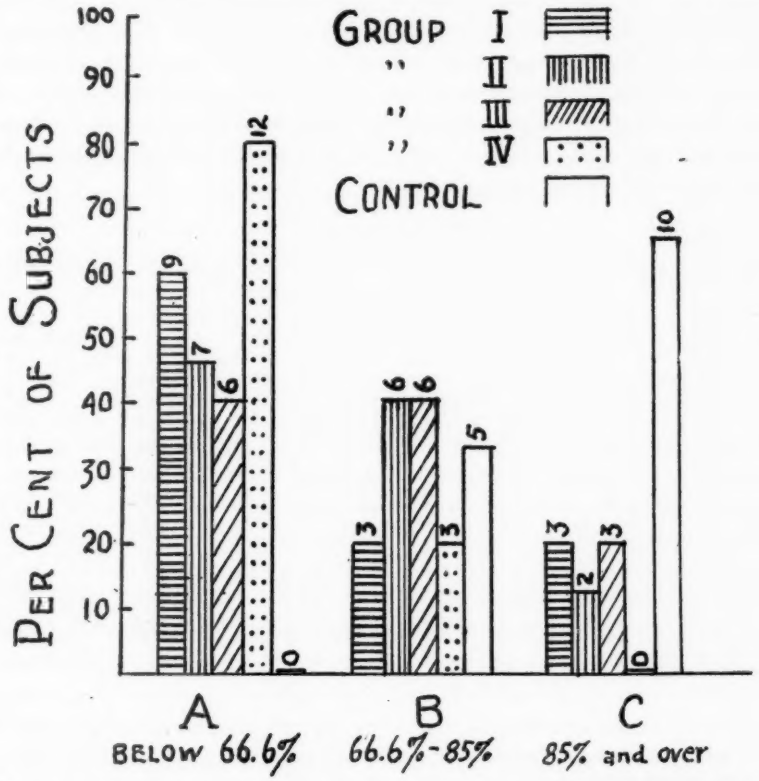

CHART 2. Relationship of each group to the different liver function values

and graph C to those of 85 per cent and over. (The numbers on top of each square represent the number of patients.)

This chart shows that individuals with a history of long-standing tuberculosis, groups I, II, IV, are represented chiefly in graph A, while history of recent infection is found in graphs B and C.

Correlation of the clotting power with the liver function test shows that the patients whose clotting power was low also had evidence of liver damage, while normal clotting power is associated with normal liver function. This again points to the major role that the liver plays in producing hypoprothrombinaemia.

Although only 31.6 per cent of the patients with pulmonary tuberculosis showed a definite hypoprothrombinaemia, a study of the effect of vitamin K was undertaken. The preparation used was Synkamin (4-amino-2-methyl-1-naphthol, supplied as the hydrochloride). It was given intravenously in doses of one and two milligrams. Bleeding time, coagulation time, and clotting power were determined immediately before the administration of the drug and were repeated in one group of patients in one-half hour, another group in one hour, a third group in two hours and a fourth group in three hours. Although no gross differences were noted in the results when performed at these different time intervals, the maximum response of the clotting power to vitamin K was produced about one hour after administration of the drug. This study is limited to the results of the immediate response to vitamin K and not to results after three hours. Table 5 presents the average values obtained in the different groups. The bleeding time, coagulation time and clotting power are given before and after administration of vitamin K, with the differences between these two values given in percentages.

TABLE 5

Average bleeding time, coagulation time, and clotting power, in per cent, before and after the administration of vitamin K

	BLEEDING TIME			COAGULATION TIME			CLOTTING POWER		
	Before	After	Difference	Before	After	Difference	Before	After	Difference
I	4′ 15″	3′ 45″	11.8	4′ 15″	3′ 30″	17.6	84.4	93.2	8.8
II	3′ 30″	3′	14.3	4′ 30″	4′	11.1	89.5	100.7	11.2
III	3′	2′ 45″	16.6	5′	3′ 30″	30.0	101.7	109.2	7.5
IV	3′ 15″	2′ 15″	30.7	5′ 45″	5′	13.0	100.0	109.3	9.3
Control	2′	1′ 54″	5.0	4′ 15″	4′	5.9	100.0	104.5	4.5

Considering the four groups of patients with pulmonary tuberculosis and calculating the average improvement produced by the administration of vitamin K, it is seen that

	per cent
Bleeding time improved	18.3
Coagulation time improved	17.9
Clotting power improved	9.2

In the control group the values are:

	per cent
Bleeding time improved	5.0
Coagulation time improved	5.9
Clotting power improved	4.5

Since the bleeding and coagulation times as well as the clotting power were within normal limits before vitamin K was administered, it can be readily understood why the response to the drug was much less marked in the control group. This supports the contention that hypervitaminosis is nonexistent, excessive

quantities being excreted rapidly by the body after a certain level has been reached.

The results demonstrate that the bleeding time and the clotting time improved almost to the same degree. At first glance this seems to be at variance with the generally accepted theory that the bleeding time, largely dependent upon the efficiency of the tissue juice and upon the elasticity of the skin, depends very little upon the chemical action of the blood. However, the results of the test indicate that the chemical composition of the blood does play a part, since the introduction of vitamin K (alteration of the blood composition) brought about a definite improvement in the bleeding time.

In analyzing the clotting power values in the different groups of patients (table 5), it is seen that group I improved only 8.8 per cent with the highest value being 93.2 per cent, while all other groups reached values of 100 per cent and over. However, when considering the results of the liver function test, which revealed abnormally low values for group I, improvements on a much higher scale could not be expected. Theoretically, vitamin K should have very little, if any, effect in the presence of extensive parenchymal liver damage, since the synthesis of vitamin K to prothrombin takes place in the liver. However, since it has been shown that clotting power values may be normal, even in the face of extensive liver damage, vitamin K should be used where it is necessary to raise the clotting power. As long as the liver dysfunction is compatible with life, vitamin K therapy is justified. This is seen in results obtained in groups II, III and IV.

The improvement of the clotting power values after the administration of vitamin K was still more striking when given to patients who were having pulmonary bleeding. It was found that the clotting power values taken during a pulmonary haemorrhage were generally lower than those taken in the same patient at other times. On an average, the clotting power values dropped between 10 per cent and 25 per cent when determined while pulmonary bleeding was occurring. After the administration of vitamin K (1 to 2 mg. intravenously) a rapid improvement of the clotting power values was observed in almost all cases. This improvement varied between 13 per cent and 35 per cent and values which were abnormally low, previous to the administration of the drug, returned to normal. In some cases, however, even though there was a marked improvement, the values remained lower than normal. As a final point, there was the immediate cessation of the haemorrhage in some patients after the injection of one dose of vitamin K. This prompt cessation of pulmonary bleeding was noted in all 14 patients to whom vitamin K was given. The bleeding was never massive, but ranged from streaked sputum to frank haemoptysis of about 40 to 50 cc. None of the patients exhibited massive haemoptysis, so the effect of vitamin K in these cases is unknown.

Finally, a study of drugs routinely administered during pulmonary haemorrhage was undertaken to determine the effect on the clotting power of the blood. These drugs were morphine and sodium pentobarbital, used in haemoptysis for their sedative action, and calcium and Koagamin for their coagulant properties.

Each of these drugs was administered to a group of 20 patients (5 from each of the four groups) and to a group of 5 controls. The bleeding and coagulation times and the clotting power values were determined before and after administration of these drugs. Morphine sulfate was given hypodermically in $\frac{1}{4}$ gr. doses and the three tests determined one-half to one hour later; sodium pentobarbital was given, by mouth, in $1\frac{1}{2}$ gr. doses and the tests determined two to three hours later; calcium gluconate (10 cc., 10 per cent) was given intravenously and Koagamin intravenously (2 cc.) and the tests determined one-half to two hours later. The results of this study are presented in table 6, with values expressed in per cent improvement.

In discussing these results it is seen that neither morphine nor sodium pentobarbital have any influence on the bleeding time, while calcium and Koagamin improve the bleeding time 7 per cent and 18 per cent respectively. The coagula-

TABLE 6

Effects, in per cent, of different drugs on bleeding time, coagulation time and clotting power of blood

		BLEEDING TIME	COAGULATION TIME	CLOTTING POWER
Morphine	Patients	0	+1	+4.25
	Controls	0	+2	+4.75
Sodium pentobarbital	Patients	−2	−16.5	−3.8
	Controls	0	−12.0	−5.7
Calcium	Patients	+7	+9.0	+6.5
	Controls	+4	+6.5	+6.0
Koagamin	Patients	+18	+12.5	+3.5
	Controls	+15	+18.0	+6.5

tion time is definitely prolonged by sodium pentobarbital, slightly improved by morphine, and still more markedly improved by calcium and Koagamin. Sodium pentobarbital reduces the clotting power considerably, morphine and Koagamin improve it in the same degree, while calcium brought about the greatest improvement. However, the improvement in the clotting power brought about by calcium does not equal that obtained after the use of vitamin K.

DISCUSSION

The results of this study show that pulmonary tuberculosis has no definite influence on the bleeding and coagulation times of the blood. In group I, the group of patients with history of recurrent haemorrhages, there was a tendency toward a prolonged bleeding time, but no actual pathological values were ever reached.

However, the study revealed that a definite percentage (31.6 per cent) of patients with pulmonary tuberculosis have a more or less marked degree of

hypoprothrombinaemia. This finding was similar to that of Scoz, Bergami and Castaldi who found that about 30 per cent of their patients with pulmonary tuberculosis showed a definite hypoprothrombinaemia. Confirmation of their finding that an even larger percentage of controls had a similar condition is lacking. They arrived at their conclusion from the findings in 13 normal persons, whereas in this study none of the 15 controls showed evidence of hypoprothrombinaemia. Stewart and Rourke found that the prothrombin level may be reduced in chronic infections, which is further evidence of the validity of the results obtained.

The results definitely show that hypoprothrombinaemia is a frequent finding in pulmonary tuberculosis and reaches the lowest values in those tuberculous patients who suffer frequent pulmonary haemorrhages. It is not believed that the hypoprothrombinaemia is the result of the frequent haemoptyses, but rather that the low clotting power is a factor in perpetuating the bleeding, once it has started. In addition, the low clotting power is the result of the failure of the liver to transform vitamin K to prothrombin, evidenced by the fact that nearly all of the patients with low clotting power had parenchymal liver damage. As already mentioned, this parenchymal damage may be secondary to toxic myocarditis or amyloidosis, both of which are not uncommon findings in tuberculosis of long standing.

The presence of hypoprothrombinaemia in patients with pulmonary tuberculosis carries prognostic significance in regards to haemoptysis, and can be used as a guide in the prophylactic treatment of this condition. Routine clotting power and liver function tests have been performed on all new admissions. When hypoprothrombinaemia is detected and there is X-ray evidence of cavities, vitamin K therapy is given. To date, no patient receiving such prophylactic treatment has suffered any haemoptysis. Of course, this is no proof of the value of vitamin K prophylactically, but future work along this line will establish its value. This prophylactic administration of vitamin K is based on the same general idea which leads obstetricians and pediatricians to give vitamin K prenatally to prevent prothrombin deficiency and haemorrhagic disease in the newborn.

The undoubted beneficial effect of vitamin K upon the restoration of normal clotting power was even still more prominent and of higher significance during pulmonary haemorrhage. Not only did the markedly abnormal clotting power greatly improve (most returned to normal values), but an immediate cessation of the haemorrhage was noted in all cases treated with vitamin K. The same observation was reported by Scoz, Bergami and Castaldi. Although these two observations indicate the definite clinical value and therapeutic effect of vitamin K in the treatment and prevention of pulmonary haemorrhage in tuberculosis, the clinical material is still too scanty to draw any far reaching conclusions.

Studying the effects on the bleeding and coagulation times and the clotting power of the blood of drugs which are routinely administered during pulmonary haemorrhage, the findings of Fitzgerald and Webster (made on patients in labor) that sodium pentobarbital causes a lowering in the clotting power was confirmed.

The use of sodium pentobarbital in pulmonary haemorrhages and in patients with low clotting power has since been discontinued. Morphine also appears to be of value in the treatment of pulmonary haemorrhage. In addition to producing the desired sedation, it also improves the clotting power to a slight degree.

The study also confirmed Schumann's report that Koagamin (active agent is oxalic acid) improves the coagulation time of the blood. A considerable improvement in the bleeding and coagulation times was noted after the administration of Koagamin. Its effect upon the clotting power was only slight.

Finally, the administration of calcium was also found to have a beneficial effect upon the bleeding and coagulation times and the clotting power. However, both Koagamin and calcium are inferior to vitamin K. Vitamin K along with morphine, therefore, appears to be the therapy of choice in the prevention and treatment of pulmonary haemorrhage in tuberculosis.

SUMMARY AND CONCLUSIONS

1. Vitamin K and its relation to pulmonary tuberculosis and pulmonary haemorrhage are discussed.

2. Bleeding time, coagulation time, clotting power and liver function tests were carried out in four groups of patients with pulmonary tuberculosis and in one control group.

3. Of the patients with pulmonary tuberculosis 32 per cent had a more or less marked degree of hypoprothrombinaemia, while there was no evidence of this condition among the subjects of the control group. Hypoprothrombinaemia is a frequent finding in pulmonary tuberculosis and reaches the lowest values among the group of patients with pulmonary haemorrhage.

4. Parenchymal liver damage was found to be present in 87 per cent of patients with pulmonary tuberculosis, while 33 per cent of the control subjects showed a slight degree of liver dysfunction.

5. Vitamin K exercises a beneficial effect upon the treatment and prevention of haemorrhage in pulmonary tuberculosis. It considerably improves the hypoprothrombinaemia which is present in nearly all cases of haemorrhage and brings about an immediate cessation of the haemorrhage.

6. The effect upon the clotting power of drugs routinely used in pulmonary haemorrhage was studied. It was found that sodium pentobarbital causes a lowering of the clotting power. Morphine, Koagamin and calcium also have a slight beneficial effect on the clotting power, although inferior to that of vitamin K.

7. It is suggested that vitamin K be used routinely as a prophylactic measure in patients whose X-ray films show cavity formation and who are shown to have a hypoprothrombinaemia.

8. Vitamin K together with the administration of morphine appears to be the therapy of choice in the prevention and treatment of pulmonary haemorrhage due to tuberculosis.

SUMARIO Y CONCLUSIONES

1. En este trabajo discútense la vitamina K y su relación con la tuberculosis y la hemorragia pulmonares.

2. En cuatro grupos de enfermos de tuberculosis pulmonar, y en un grupo testigo, se hicieron estudios relativos al tiempo de hemorragia, al tiempo de coagulación, la facultad coaguladora y la función hepática.

3. Un 32% de los tuberculosos pulmonares revelan una hipoprotrombinemia más o menos intensa, aunque no hay signos de este estado entre los testigos. La hipoprotrombinemia constituye un hallazgo frecuente en la tuberculosis pulmonar, y alcanza sus cifras mínimas en los casos en que hay hemorragia pulmonar.

4. En 87% de los tuberculosos pulmonares observáronse lesiones del parénquima hepático, en tanto que 33% de los testigos revelaron una notable disfunción hepática.

5. La vitamina K ejerce un efecto beneficioso en el tratamieñto y profilaxia de la hemorragia en el tuberculoso pulmonar. Hace mejorar considerablemente la hipoprotrombinemia que existe en casi todos los casos de hemorragia, y cohibe casi inmediatamente la hemorragia.

6. En un estudio del afecto de las drogas empleadas habitualmente en la hemorragia pulmonar sobre la facultad de coagulación, observóse que el pentobarbital sódico hace subir dicha facultad. La morfina, la coagamina y el calcio también ejercen un ligero efecto beneficioso sobre la facultad de coagulación, aunque inferior al de la vitamina K.

7. Indícase, pues, que se emplee sistemáticamente la vitamina K como profiláctico en los enfermos cuyas radiografías revelan cavernas y que manifiestan hipoprotrombinemia.

8. En la profilaxia y tratamiento de la hemorragia pulmonar debida a tuberculosis, la administración de vitamina K, junto con morfina, parece ser la terapéutica de elección.

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VOCATIONAL THERAPY[1]

The Program at Municipal Sanatorium

EDGAR B. PORTER[2]

Starting a paper of this kind on a pessimistic note can be justified only because it serves as a basis for comparison and also as a fitting introduction to more optimistic thoughts to follow.

John W., aged thirty-three, single, had been employed regularly since 1924, first as a shipping clerk, then as a machinist and finally as a school janitor. In 1933 he broke down with pulmonary tuberculosis. He had had four different periods of hospitalization prior to his discharge from Municipal Sanatorium in November, 1938. Since no serious effort had been made prior to his discharge to consider his need for vocational readjustment, his written testimony, given to the Rehabilitation Bureau about two and one-half years after discharge, may be fairly typical of the experiences of countless numbers of ex-patients discharged annually from tuberculosis sanatoria all over the country.

"Shortly after my return from the sanatorium in 1938, I was called to the State Employment Office, but they said they could not classify me in regards to being placed in employment due to the fact of my having tuberculosis. I tried independently to obtain work but without success. My condition was fairly good at the time and I believe I could have worked had I the opportunity. After a few months the physical condition was not so good and is the same at the present time, so much so that the clinic doctor has advised me to return to the Sanatorium. I don't believe it would be of any use at present to visit the Bureau as I am waiting for admission to the Sanatorium. However, it would be a big consolation to know that upon my return I would stand a chance of securing a job, and not face the conditions as they were on my last return from the Sanatorium. I believe if most of the ex-patients were able to secure employment of the right sort there would be less relapses and inevitable returns to hospitals and sanatoria. This, of course, is only my humble opinion. Hoping the contents of this letter may be of help to others as well as to myself. . ."

It is useless to do more than apologize for the lack of attention given in past years to the problem of readjustment facing the tuberculous. Suffice it to say that detecting the disease and arresting its progress has to date represented more than a full-time job. There is a general feeling, however, that we are now entering an era when responsible authorities, in their desire to conserve man power, will place a sanatorium vocational therapy program in a position of equal prominence with procedures designed to detect the disease and to arrest its progress.

Probably the most important justification for vocational rehabilitation work in a tuberculosis sanatorium is found in the effect of such a program on speeding the patient's early recovery. Physical idleness, which is a necessary part of

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early treatment of the disease, must find its therapeutic counterpart in carefully regulated activity designed to restore work habits and to re-create general work abilities. It is felt, therefore, that there is no substantial disagreement with certain basic assumptions which were, as a matter of fact, accepted as justification for the interest of Municipal Sanatorium in setting up its rehabilitation program.

It would be well at this point to restate these assumptions which, it is believed, are now widely accepted by that part of the medical profession specializing in tuberculosis work:

1: A well rounded program of medical supervision of the tuberculous patient has not reached completion until the patient has recovered sufficient work tolerance to permit him to take his place in economic life where he is again able to be independent in a carefully selected occupation in competition with the able-bodied.
2: Mental and physical activity provides a standard by which the physician can measure the patient's work tolerance. Also, such activity, prescribed wisely, and with the approval of the physician in charge, will, in most instances, contribute to a speedier recovery than would be the case if the patient continued to carry on a life of comparative inactivity.
3: A speedy return of the patient to suitable employment when physically ready may provide one important safeguard against the growth of conditions that bring about relapse and subsequent rehospitalization.
4: For medical and economic reasons, therefore, rehabilitation in the sanatorium should occupy a place of major prominence alongside other techniques used in treatment. Thus the patient will derive maximum benefit from his sanatorium stay and a contribution will have been made to the total plan of returning the patient to a satisfactory economic status in the shortest period of time.

A suitable program for the vocational and economic readjustment of tuberculous patients has been the subject of study at Municipal Sanatorium, Otisville, New York, since the spring of 1938. Under the direction of the State Vocational Rehabilitation Bureau, it has been the object of practical demonstration since September, 1940. While sufficient time has not elapsed to produce a statistical evaluation of results, a discussion of the objectives of the program, as well as the methods of organization, may provide some helpful suggestions to other tuberculosis sanatoria and hospitals interested in setting up a similar program.

The make-up of the patient population and, therefore, its needs are not the same for any two institutions. In starting the program, therefore, it is essential, as a first step, that a survey of the patient population be made to determine what its peculiar needs may be.

Such a survey was made by the State Rehabilitation Bureau at Municipal Sanatorium in 1938, in coöperation with the New York City Department of Hospitals. Histories of 500 patients were secured. The following statistics bearing on the needs of the program to be inaugurated were assembled as a result of the survey:

1: Sixty per cent of the patients surveyed were thirty years of age or under. This means that a majority of the patients were at a desirable age from the standpoint of employability.

2: The medical status of the patients seemed to point to the prediction that a large majority would get well and would therefore be able to reënter employment.
3: The educational background of the patients was an important factor. Suitable jobs in which arrested tuberculous cases may be reëmployed are most likely to be found in fields based on skills requiring at least a fair amount of school education. In 74.8 per cent of the cases, patients had an education of eight grades or better.
4: Previous vocational training in preparation for suitable employment is undoubtedly one key needed to open the door to job opportunities; 62.4 per cent of the patients surveyed had no organized training in preparation for an occupation and, of this group, 61 per cent were less than thirty years of age. Without proper job preparation many of the tuberculous will undoubtedly be compelled to accept employment inconsistent with their physical condition.
5: It was found that 29.4 per cent of the patients surveyed were in need of complete or brush-up vocational training, either to change to a new occupation or to learn skills required for a first job, or to relearn skills needed to return to a previous suitable job. Of this group, 33.3 per cent were students or young persons out of school with no previous work experience; 22.4 per cent were manual laborers who were employed in occupations unsuitable from a physical point of view; 23.8 per cent were semi-skilled workers; 22 per cent were skilled workers. In the last two groups a careful analysis of the previous occupation was essential to determine its suitability with respect to the physical condition.
6: It was found that 42 per cent of the total were not employable without some rehabilitation service and, of this number, 85.2 per cent had great need for such service.

A survey procedure similar to the above would appear to provide the necessary background for a rehabilitation effort in any institution.

Having determined the general make-up of the entire patient population of the sanatorium, it was then necessary to secure first-hand knowledge of the problems of each patient with respect to his particular needs. Nothing could be further from the truth than the statement heard in some quarters that all those afflicted with pulmonary tuberculosis do, by virtue of that fact, require special retraining services looking to a change of occupation. The problem of the after-care of this group of disabled persons is too complex to permit of any such "easy" solution. Careful analysis of the background of each patient will show that he can be placed in one of seven groups, with respect to need for assistance in becoming vocationally readjusted to employment. Steps should be taken to determine:

1: Whether he is in need of vocational training, because prior to breakdown he had no specific skills nor substantial work experience.
2: Whether he is in need of vocational retraining, because from the standpoint of health hazard the previous occupation is unsuitable.
3: Whether he is in need of training which will enable him to brush up skills possessed prior to breakdown.
4: Whether he was, prior to breakdown, employed in a suitable job for which he possesses the requisite skills, in which he is experienced, and to which, from the standpoint of health hazard, he may safely return.
5: Whether the patient is a housewife and, as such, is likely to return home without any specific employment need except as a factor secondary to her home interests.

6: Whether, because of advanced age, lack of education, nature of previous work experience, advance of disease, or a combination of several of these factors, he is (*a*) not suitable for vocational training or retraining; and (*b*) not employable in competitive employment. (Here we have a combination of employment, custodial care and permanent sheltered employment.)
7: Whether he is questionable from the standpoint of recovery prognosis, and therefore represents too great a risk to attempt a vocational readjustment. He will probably require continuous medical care.

Following a complete and careful analysis of each patient's background, interests, personality and ambitions, he can be placed in his proper group. Such a procedure points immediately to the nature of the future rehabilitation plan. It delimits the whole problem of adjustment of the tuberculous and permits major emphasis being placed on working with those patients who may need special assistance.

Reference has often been made to the close relationship that should exist between medical and rehabilitation services. To bring about such close coöperation requires knowledge on the part of both services of the steps the patient should take chronologically to make his economic comeback. Thus there will be set forth in bold relief that part of the entire rehabilitation job which should rightfully be assigned to the period of hospitalization.

From onset of disease to final return to an independent economic status the following steps should be taken, in order; the last two steps presuppose that the patient's need is to return to suitable employment:

1: Initial bed-rest and treatment that will carry him to the point medically where consideration can be given to some directed activity.
2: Interviewing to secure acquaintance with his educational and vocational background, so that his future needs may be clearly understood.
3: Outlining a tentative program consistent with knowledge of his background, and looking forward to vocational readjustment consistent with his disability and abilities.
4: Assigning him to an activity in the sanatorium, with medical approval, which is in line with his interest, and which will, if possible, have the dual effect of maintaining his morale and helping him progress toward his vocational goal.
5: After discharge, making certain that he is under adequate medical supervision.
6: Under careful supervision, and with medical approval, assigning him to a work activity which is consistent with the vocational plan outlined, or revised, in the sanatorium, and which will contribute to increasing his work tolerance, at the same time advancing him still further toward his vocational goal.
7: When medically approved, referring him to the appropriate agency for retraining or employment service, or both, in accordance with his needs and in line with his vocational goal.
8: Following up his progress after he has become employed to determine whether or not he has made a satisfactory vocational adjustment consistent with his health and economic needs.

It is essential that many of the tuberculous be assisted in taking each step along the way. This program does not by any means represent the easiest or

least expensive way, but it is felt that on the effectiveness of the assistance given the patient in taking each step will depend the success attained by the tuberculous in solving his vocational problem.

The rehabilitation program now in effect at the Municipal Sanatorium can best be visualized by describing the various steps in the progress of each patient from the time of referral by the physician to the date of discharge.

An ideal program would involve starting the rehabilitation process as soon as possible following the patient's admission. This procedure would prevent the formation of attitudes and mental habits usually associated with physical rest unaccompanied by mental activity. For purposes of demonstration, however, the first contact with the patient at Municipal Sanatorium has been made after the physician has indicated that the patient is ambulant and is therefore physically ready for a limited amount of work activity. The physician supplies information regarding the length of disability, stage of disease, condition, other physical complications, prognosis for recovery and amount of work activity permitted daily. The social service department and the nursing division are asked to supply information growing out of contacts with the patient. The rehabilitation worker, through an interview with the patient, supplies further data relating to education, special vocational training and work experience, and gains further knowledge of interests, avocations, ambitions, vocational desires, character and personal appearance. As a part of the analysis, it is often found necessary to administer psychological aptitude tests, and the experience at Municipal Sanatorium shows that approximately 50 per cent of the patients referred have been so tested. All the essential information is summarized in such a way as to give a clear picture of the patient's future vocational needs, if any. This summary is presented to the vocational conference, at which time a recommendation is made and a suitable sanatorium work activity assigned.

A statement regarding the vocational conference may be in order at this point. At regular intervals conferences are held, which are attended by the medical superintendent, the entire medical staff, occupational therapist, social worker, the superintendent of nurses and head nurses, the psychologist and the director of rehabilitation. As each case is presented for discussion, the first point of reference is to the patient's X-ray films and medical chart, on the basis of which the doctors state whether or not the patient is at that time physically ready for work. If he is, the director of rehabilitation presents his summary and recommendation. Always the rule is to seek a work activity in the regular sanatorium set-up that will be in line with the patient's estimated vocational needs, as well as with the general type of work in which the patient is expected to engage following recovery. A discussion of the variety of work activities organized at Municipal Sanatorium will be touched upon later in this article.

Following the conference the decision as to work activity is summarized and directed to the attention of the sanatorium official assigned to the supervision of the patient in that activity. Space is provided at the bottom of the form in use for the physician's approval or disapproval. The physician is thereby given the opportunity to indicate the maximum number of daily hours the patient is

permitted to engage in that activity. This procedure guarantees medical control of the entire program by the physician who is directly responsible for medical supervision.

Approximately once each month a report is requested from the supervisor. Aside from indicating progress made, opportunity is afforded to indicate problems that have arisen. This progress report is presented to a subsequent vocational conference and the activity previously assigned is either continued or changed to something more suitable. It often happens that, through the activity to which the patient is assigned, further information is obtained regarding abilities, skills, attitudes and interests which may point to a change in the vocational objective and activity previously decided upon. Again the physician is given the opportunity to indicate increased hours of activity permitted, or may order that the activity be interrupted for physical reasons. The patient is again presented for activity when the physical condition has improved.

Prior to discharge the patient is again brought up at a vocational conference for a discussion of what has been accomplished in the activity to which he has been assigned and also to indicate the logical next step in his rehabilitation. Upon discharge, information relating to the medical status and the sanatorium rehabilitation program is summarized and sent to the clinic responsible for medical after-care and follow-up, as well as to the community organization responsible for helping the patient take his next step toward vocational readjustment.

In general, it is felt that the program at Municipal Sanatorium is unique in the sense that activities inherent in the administrative set-up of the institution are being utilized in providing patients with a wide variety of work experiences. It should be kept in mind that a serious attempt has been made to assign each patient to an activity which, in its content and training values, is related to his future employment needs, if any. It should be observed that those with no apparent vocational needs, such as housewives and those who can return to their former occupations, have not been neglected. It is felt that a rehabilitation program in a sanatorium or hospital is of wider significance than a mere return of the patient to suitable employment; it undoubtedly has therapeutic value of which all patients who are physically able should take advantage.

Occupational therapy takes its rightful place as an important part of the program. The value of permitting each patient to take part in a pleasurable activity has not been lost sight of. At the same time it is felt that the assignment of each patient to a type of work that is purposeful in terms of a future employment objective is pleasurable because it is meaningful and directional. Thus the patient's assignment to occupational therapy is in terms of an activity that is a vital part of the entire plan for his rehabilitation. This point of view has brought about a distinct improvement in what has traditionally become known as "occupational therapy."

The use of supervised correspondence courses has been experimented with to some extent. An agreement is in effect with a well known correspondence school which provides for a three-months contract at a flat rate. This plan permits the

patient to cover as much or as little of the entire course as his mental and physical condition permits. Such courses are, however, reserved for patients who will be good risks and who possess the initiative and ambition to profit by them.

A group interested in the practical and theoretical phases of photography has been organized. This group is visited by a volunteer lecturer from a nearby city.

A teacher from a nearby public school system has been engaged to teach commercial subjects.

There has been found among the patient group one or two college graduates qualified to teach English to foreigners.

Group lectures on home economics are given by the head dietician of the Sanatorium to present and future housewives.

Those involved in the maintenance set-up of the institution, such as the maintenance foreman, the electrician and the tinsmith, are coöperating in relating their functions to the interests of certain patients.

Thus the resources of the administrative organization of the institution as well as those of the patient population are utilized to the mutual advantage of all.

It is not the primary purpose of this discussion to list the names of the various activities to which patients have been assigned. Such a discussion might properly be left to a complete paper on the relationship of occupational therapy to the entire problem of the vocational readjustment of the tuberculous. It may be sufficient to state at this point that in the program at Municipal Sanatorium sixty-four activities or combinations of activities have thus far been utilized.[3] Again it should be emphasized that each activity has, insofar as practicable, been related to the specific vocational or diversional need of each patient. This, in the opinion of those now administering the program, is occupational or vocational therapy in its best and most forward-looking sense.

A university is known by its alumni. In the same sense a vocational therapy program in a tuberculosis sanatorium must depend for its justification on the satisfactory adjustment made by those who have been subjected to its benefits. While sufficient time has not elapsed to evaluate the effect upon large numbers, the experiences of a few may serve to illustrate the purposeful direction the program has taken.

A young man who, soon after discharge, secured a full-time office position, was encouraged in the sanatorium to brush-up on his office skills through the medium of the office training class.

A young lady who planned to return to her former position involving switchboard operating was assigned for activity at the sanatorium switchboard. Following her discharge, she returned to her former job.

A fifty-year-old man was assigned to typing in order to supplement his former experience as a general office worker. Following discharge, he secured reëmployment as a supervising clerk in an administrative office.

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[3] The list of activity assignments at Municipal Sanatorium can be had from the author on request in mimeographed form.

A young lady who qualified for a civil service appointment as a hospital attendant was given the opportunity to secure experience in the sanatorium X-ray laboratory.

A young medical student who planned to return to medical school following recovery was assigned to the clinical laboratory for intensive instruction in laboratory techniques.

The experiences submitted will doubtless be multiplied in number as the program develops. Compare the experiences of these patients with the outlook facing the patient whose letter was quoted at the beginning of this paper! Thus we can close on an optimistic note! The methods used and the objectives set up may very well stimulate progress in the thinking and practices of forward-looking occupational therapists. In the past the emphasis has been placed on the word "therapy." In the future the word "occupational" must be stressed, if occupational, or *vocational*, therapy is to make a more realistic contribution to the *clearly understood vocational needs* of patients in our tuberculosis sanatoria and hospitals.

SUMMARY

In the fall of 1940 a rehabilitation program was begun at the Municipal Sanatorium under the direction of the New York State Rehabilitation Bureau. Such a program was not initiated haphazardly, but was based upon the results of a survey made in 1938 of the patient population then at the Sanatorium. The justification and organization of the program are described in detail. Step by step the patient is followed from the time of referral by the doctor to initial interview, collection of data concerning him from other sources, possible subjection to psychometric testing, estimation of future vocational needs and a vocational conference, at which time he is assigned to an activity in the sanatorium in line with his vocational need. Only a few new activities have been set up; most of them are incorporated in the administrative and patient set-up of the Sanatorium.

SUMARIO

En el otoño de 1940 inicióse en un Sanatorio Municipal una obra de rehabilitación bajo la dirección de la Oficina de Rehabilitación del Estado de Nueva York. Esta obra no fué iniciada al azar, sino que se basó en el resultado de un censo de los enfermos que había en 1938 en dicho Sanatorio. Expónense minuciosamente la justificación y organización de la obra, y enuméranse los distintos pasos a que se conforma la observación del enfermo desde la entrevista inicial después que lo encamina el doctor al Sanatorio, con la recolección de datos obtenidos de otras procedencias, posible aplicación de la psicometría, apreciación de las futuras necesidades vocacionales, y la conferencia en la cual se determina qué trabajo del Sanatorio se conforma mejor a sus necesidades vocacionales. Sólo se han establecido algunas pocas actividades nuevas, pues la mayor parte ya están incorporadas en la organización administrativa y curativa del Sanatorio.

VOCATIONAL THERAPY IN THE SANATORIUM[1]

The Medical and Administrative Phases

I. D. BOBROWITZ[2]

The organization and technique of the vocational therapy program at the Otisville Sanatorium has been very thoroughly and ably presented by Mr. Porter. I would like to discuss some of the medical and administrative phases of this activity.

First, for a proper interpretation of our program, some information about the institution is desirable. The bed capacity is 400, with an occupancy of 98.4 per cent. There are about 50 discharges and 50 admissions each month. The statistics for the first eight months of 1941 reveal that, of the patients admitted, 50 per cent had minimal, 44 per cent moderately advanced and 3 per cent far advanced disease. The use of collapse therapy is extensive, with 30 per cent of the patients receiving pneumothorax, and 58 requiring Jacobaeus operations. Three patients had phrenic operations this year, and 28 post-thoracoplasty cases were treated. The daily average number of infirmary and semi-infirmary cases is 180. Of the patients discharged, 81 per cent benefited by their hospitalization, with 38 per cent arrested, 17 per cent apparently arrested, 16 per cent quiescent and 10 per cent improved. The percentage unimproved was 12.5 per cent and 4 patients (1.09 per cent) died. The average stay of all patients discharged, including those against advice, was 7.75 months, and the stay of patients discharged by the Medical Board was 8.8 months.

Vocational therapy has too often been neglected entirely, or treated indifferently as an unimportant and unproductive service in which patients idle time away. There has been a consequent lack of interest in its development. This attitude has resulted principally from a failure to understand the true value and need of rehabilitation and the necessity of its integration in the essential functions of the sanatorium. It is of serious import, therefore, to emphasize the imposing number of significant reasons that denote the essential usefulness of rehabilitation.

Both mental and physical factors are included in the functions of a vocational therapy program.

The mental benefits patients may obtain from participation in this plan are many. Invariably, the patient's morale is bolstered with the knowledge that increased activity is associated with an improvement of the physical condition and betterment of the disease process. The actual engagement in regulated work relieves the boredom and monotony of a prolonged and otherwise unvaried period of sanatorium care. There are opportunities for desirable and pleasant social contacts. There is mental stimulation with the new interest in creative

[1] Presented at the meeting of the American Occupational Therapy Association and American Congress of Physical Therapy in Washington, D. C., September 4, 1941.

[2] Municipal Sanatorium, Otisville, New York (one of the institutions of the Department of Hospitals of the City of New York).

work and the relaxation through diversional efforts. Patients who were non-coöperative in their care, irresponsible and lacking confidence in themselves, have by this program been properly adjusted psychologically. Both the non-employable and employable patients require and obtain the mental assurance and optimism that comes only to those with a definite capacity for physical activity. The latter group, especially, with the promise of economic self-sufficiency, can survey the future, not with the pessimism and despair of a hopeless outlook, but rather with buoyant faith and cheer. The approaching period, after discharge from the sanatorium, becomes not a clouded dismal question mark, but rather a clear vision of a normal, self-supporting life.

The gradual increase in exercise and work by the patient characterizes rehabilitation as ergotherapy. Though the arrest of the tuberculous process is the primary function of the sanatorium, the attainment of this status is not the entire goal of treatment. It is necessary for the patient, after discharge, to be in condition to continue sheltered work or additional skilled training, or to be able to accept the activities of industrial employment or the responsibilities of a normal social life.

The patient can obtain a physical status to permit such activity after discharge, only by the therapy of work. A supervised graded development of work capacity will gradually improve the patient's exercise tolerance, and accustom the pulmonary, circulatory and muscular systems to increasing loads of exertion. The individual's strength and energy thus grow progressively.

Ergotherapy, in its own right, is as necessary as collapse treatment or any other method of care for tuberculosis. It extends far beyond the mere testing of a patient's physical endurance. It is a scientific method, physiologically sound, of gradually improving the physical condition.

It is an aid in the recovery of tuberculosis by constituting a controlled convalescence. A diagnosis of the arrest of a tuberculous process cannot and should not be made unless stability of the diseased area is present under conditions of supervised activity. Such a diagnosis can be made safely only with a regulated program of ergotherapy. This principle is exemplified by the controlled convalescence in the treatment of rheumatic fever wherein freedom from symptoms must be associated with increasing exercises. Likewise, in tuberculosis, the fundamental purpose is to increase the work tolerance without the occurrence of dyspnoea, fatigue or other symptoms or evidence of clinical activity, and the maintenance of a stable lesion by X-ray. Ergotherapy is indicated, and the physiological benefits will result, whether the original treatment for the tuberculosis was bed-rest or some form of collapse therapy.

Patients should not be discharged from the sanatorium without knowledge of their work tolerance. It is relatively simple to gradually increase the work requirements after discharge with a record of regulated sanatorium activity as a guide, and it is difficult to do this without the sanatorium experience. Without this preparation, the patient cannot readily become adapted to the normal energy requirements of activity after discharge, and certainly not to sudden physical demands. Moreover, patients not prepared for employment may accept un-

suitable jobs. In this manner, the lack of ergotherapy in the sanatorium, uncontrolled activity after discharge and improper after-care, with acceptance by patients of physical burdens with no definite concept of their ability to withstand these efforts, weaken the pulmonary tissue and function to a degree that a breakdown may result. Not in a small measure is the present high percentage of relapses and sanatorium readmissions caused by this sequence of events.

Besides the numerous advantages for future employment and proper social and economic adjustment after discharge, as stressed by Mr. Porter, the mental and physical benefits indicated above warrant the conclusion that vocational therapy is not a luxury but a necessity and it should represent an integral part of the accepted functions of the sanatorium in the therapy of tuberculosis.

Rehabilitation should be started as soon as the patient's physical condition permits an acceptance of activity. A simple, practical method to guide medically the assignments of the patients is one in which, as at the Municipal Sanatorium, numerals from zero to eight are used for the classification of activities. This arrangement is based on the need for bed-rest and the capacity of the patient to engage in ambulatory functions and vocational therapy.

Activity 0 = Absolute bed-rest.
Activity I = Patients on bed-rest with bathroom privileges.
Activity II = Patients allowed to have meals in the dining room on the wards. Remainder of the time at rest.
Activity III = Patients in ambulatory pavilions attending the main outside dining halls for meals three times a day. Perform various ward duties. May attend church and recreational hours and movies.
Activity IV = Same as activity III, plus vocational therapy, one-half to one hour daily.
Activity V = Same as activity III, plus vocational therapy, one to two hours daily.
Activity VI = Same as activity III, plus vocational therapy, two to three hours daily.
Activity VII = Same as activity III, plus vocational therapy, three to four hours daily.
Activity VIII = Same as activity III, plus vocational therapy, four hours or more daily.

The general criteria for the placement of patients in this program include the following:

The treatment, activity or hospitalization that preceded admission to the sanatorium may indicate the work tolerance of the patient.

The type and extent of pulmonary involvement is important. A stable or retrogressive lesion according to X-ray or an absorbing or absorbed effusion is required. A longer wait before assignment will occur in patients with cavity or in those with soft lesions, than in patients with old or fibrotic processes. In patients who have had collapse treatment of the lungs, the effectiveness of these measures must be evaluated.

The patient must be afebrile and not toxaemic.

There must be no contraindicating medical or surgical complications, or physical findings.

The sputum concentrations and gastric contents must be negative for tubercle bacilli. Almost invariably, the sputum cultures are also negative. However,

an occasional exception will be made of patients with positive cultures if there is no evidence of any other change to indicate clinical activity of the disease or progression of the lesion.

The satisfactory fulfilment of these factors is not the only requirement for placement in the program. For proper physical preparation before assignment to rehabilitation, the patient has been for a few weeks at least in an ambulatory pavilion and on activity III. If the energy requirements of this regimen produce no contraindications, then most patients are started on one hour daily of actual work in vocational therapy. Depending on the factors enumerated above, a few patients may have more or less than this time as an initial allowance. As the patient's condition improves, with no untoward results, the physical activity is gradually increased. In this way, most patients can be worked up to at least a four-hour work tolerance when discharged.

Patients with active or hopeless disease are excluded, but vocational therapy may be applied at the bed-side for patients who, though not ambulatory, are able to assume a certain measure of physical activity while in bed. This can be in preparation for additional work in the future, and is also of value in itself for the improvement in mental attitude it provides.

Nothing takes precedence over the medical and surgical indications for treatment of the tuberculous process and the physical condition of the patient. The vocational program must be stopped or altered to suit the medical or surgical need. The statistics for the medical supervision of this program are not complete, but preliminary observations can be made.

Of 300 patients considered at vocational conferences, 277 were assigned to activity, and of these, 38 or 13.7 per cent were removed from the program at later conferences; 13 of these subsequently resumed their activity, so that actually, 9 per cent of the patients originally assigned are out of the program. The reasons for the removal of these patients from activity were as follows:

Positive culture	7
Positive sputum	7
Positive gastric lavage	7
Progression of lesion	6
Increase of symptoms	3
Jacobaeus operation	3
Change in chest fluid	2
Gastric ulcer	2
Perineal (nontuberculous) abscess	1

Their removal from vocational therapy occurred at the following periods after assignment:

One and one-half months	10 patients
Two months	11 patients
Three months	6 patients
Four months	4 patients
Five months	3 patients
Six months	3 patients
Seven months	1 patient

Of the 13 patients reassigned, one was returned in two weeks, 5 within one and one-half months, 4 within two months, one in two and one-half months and 2 within four months.

Careful medical control of vocational therapy is very necessary, and the progress of the patients must be closely reviewed. There is risk in the premature assignment of patients. The general criteria, outlined above for the placement of patients in the program, must be followed, but each patient must be considered not so much by group criteria as by individual indications. The fact that no patients were removed till after one and one-half months would signify a deliberate selection of cases. It is also apparently true that it rapidly becomes evident if the increase of activity is properly tolerated. Half of the patients were removed within two months, and three-quarters of them within three months. The causes for a change in physical status are often temporary, however, as exemplified by the 13 patients who soon resumed their activity. Five patients have been discharged and some of these may have had their assignments renewed. Not all of these activity changes resulted from the work in vocational therapy. This is evidenced by the 3 patients who had elective operations (intrapleural pneumonolyses), the 2 with nontuberculous gastric ulcers and the one with a nontuberculous (perineal) abscess. The fact that over half of the patients had their activity stopped because of positive cultures or sputa or gastric lavages is also important. The sputum examination procedure used in the Sanatorium is very exhaustive, particularly in reference to the number of gastric lavages and cultures. Under ordinary laboratory requirements, even if the standards of the National Tuberculosis Association were followed, many of these patients would have had their activity continued. It is our policy to give the patient the benefit of every possible doubt, and they are removed from work if there is any question of danger.

Twenty-three of the 300 patients, or 7.6 per cent, were not approved for assignment at the first vocational conference. The statistics presented cover the period up to August 15, 1941, so that a number of those recently removed will be eligible soon to resume their activity. Moreover, some patients who have reached an ambulatory status, but are not yet assigned to rehabilitation, are also required to have their activity reduced. Our figures, then, would indicate that rehabilitation is not a medical hazard.

For medical reasons, it is impossible for sanatoria to continue hospitalization and rehabilitation until the patients are on a work tolerance of eight hours a day and acceptable for placement in outside industry. A condition of arrest for the tuberculous process (the criterion for discharge) is reached long before that time and usually when the patient is on activity of a few hours daily. It is necessary for the establishment of a routine plan whereby patients referred to sheltered workshops or employment bureaus will be accepted if arrested and on a part-time work basis. In this way, unduly prolonged hospitalization could be avoided and immediate rehabilitation follow-up after discharge furnished. It is not logical or wise to expect sanatoria to do more than this in vocational therapy. This program will fail if its success depends on the preparation of

patients by the sanatorium for full time work. If industry will not accept patients otherwise, then there is a definite and urgent need for State or Federal subsidy or support by welfare or health associations of industrial establishments or training centres to receive part-time patients for work or instruction.

There is unfortunately no unanimity on the question of the importance of rehabilitation in the sanatorium. There are many who believe it is not related to the functions of the sanatorium and that it should be planned for after hospitalization. It is still necessary to sell vocational therapy to the staff and the patients. This can occur with a thorough and persistent educational scheme.

To inaugurate properly and utilize successfully a vocational therapy plan, it is necessary to procure and maintain the sincere interest, complete coöperation, full understanding and untiring efforts of the staff.

The educational scheme for the hospital personnel should include talks at group conferences by members of the staff who are associated with the program. The benefits of rehabilitation and the dependence of the success of the department on the coöperation, enthusiasm and effort of the participants should be emphasized. Conducted tours through the occupational therapy shops and other units in the rehabilitation division should be planned. Case illustrations and lantern slides and motion pictures on tuberculosis and rehabilitation, particularly those furnished by the National Tuberculosis Association, will make the lectures more interesting and enjoyable. Talks at medical board meetings and a complete account of the program in the sanatorium annual report will focus attention on the problem of rehabilitation. The employment phase can be presented by the State Rehabilitation Worker or the individual acting as a liaison for the employment agencies.

The educational program for the patients should include, besides individual contact between them and the various members of the hospital personnel, lectures to the entire patient group with the use of slides and moving pictures. Always, the practical usefulness of all the activities of this department must be stressed. There are especially several opportunities for contact between the patient and resident physician: on admission to the sanatorium, at the time of transfer from one ward to another for increased activity, and when the patient is assigned to rehabilitation work. Letters can be presented from patients in the sanatorium, or discharged, that describe their satisfaction with the program and its benefits. Articles for the patients' magazine are also important. The patients should become rehabilitation-minded.

Several questions are repeatedly presented by the patients worthy of comment. They often cannot associate the aims of the program and the emphasis that is placed on rest as an important part of their medical treatment. There is a fear of activity. The gradual assignment to increasing demands of work and the close medical control of the program must be explained and especially the preparation of the patient for a proper sanatorium discharge and activities in the home or in industry.

Contrariwise, some patients, because of their assignment to an ambulatory status and increased activity, conclude that their physical condition must be

excellent and that they need no further hospitalization, and they discharge themselves from the sanatorium against medical advice. The need of proper rehabilitation guidance and the importance of uninterrupted treatment till discharge in an arrested condition should be stressed, and the clinical axioms repeated that (*1*) the continuation of a satisfactory status after discharge is more probable the closer the patient is to a condition of arrest before leaving the sanatorium, (*2*) the future prognosis is definitely poorer for patients who sign out, and (*3*) arrested cases represent the majority of those patients who are able to return to work after discharge.

Occasionally, patients will fail to coöperate because they conclude that their assignment to various positions in the shops, offices and sanatorium departments is a method of exploitation and of saving of paid hospital personnel. Constant emphasis must be made of the value of rehabilitation as treatment for the patient, with personal gain to the patient by the activity, and of the dependence of the sanatorium for the maintenance of all its services and functions on regular personnel only with no need for patient labor.

Some rehabilitation programs permit small financial payments for a few of the patient positions. This may have the undesirable consequence of the patient's placing more importance on the payments than on the value of the vocational therapy and the coöperation of the patients may thus be adversely influenced. It is necessary to stress repeatedly to the patients that their work in rehabilitation is not primarily for financial gain but to help them get well.

There are a few other medico-administrative problems associated with the program that may be mentioned, and these can be grouped under several general subdivisions.

Procedures: Occasionally, staff members are prompted, after personal discussion with, or requests of, the patients, to change their assignments. To maintain proper control of the plan and to offer the patients the benefit of staff opinion, no changes in work activity recommended at the conferences should occur without discussion at a conference.

To have readily available the coverage of the vocational therapy department, a list can be kept of all the assignments with the number of male and female patients engaged in each category and the quota of positions desired.

For a successful and smoothly working program, attempts should be made to have each vocational therapy function include patients with sufficient experience and training to aid the therapist in teaching other patients, so that as the more efficient and experienced patients are discharged, others will be able to assume the responsibilities of the assignment. If this constant teaching is not planned or if no regulation of the sanatorium discharges is instituted, all or most of the patients included in a particular project may be discharged simultaneously and teaching of an entirely new group will be required. In the meantime, certain phases of the Vocational Therapy Department may temporarily be at a standstill. To avoid such occurrences, prior to the presentation of a patient to a staff physician for discharge, a notation should be sent to the Vocational Therapy Department and the administrative office with the name of the patient, the rehabilitation assignment and the expected date of discharge. With this

information, the vocational assignments and discharges can be satisfactorily arranged and regulated.

To avoid delay in the assignment of the patient after recommendation has been made at the vocational conference, all the division heads should be routinely advised to call for the patients without waiting and to follow out the suggestions made. An immediate report and check-up follows for any patient who does not respond to an assignment. The resident physician should be notified concerning any patient who does not adhere to the schedule and the division heads informed of any patients who cannot report. The physician should interview the patient about the necessity of strict adherence to the schedule of visits outlined.

Records: Besides the information on the regular rehabilitation form already described, the patient's clinical chart should contain notes each time the patient's physical activity is changed and data about the amount of time spent on rehabilitation, the type of assignment and the tolerance to and the interest in it.

Follow-up: To avoid misunderstandings with the hospital or health clinic or private physician providing postsanatorium care about the amount of activity to be pursued by the patients after discharge, these agencies should routinely be provided with a complete medical abstract and the pertinent rehabilitation features of the case and representative X-ray films. This will definitely diminish the chance of disagreement with outside agencies about the sanatorium recommendations for rehabilitation and permit the patients' rehabilitation work to continue at a proper level of physical activity. The medical person who has had the patient under constant supervision for the greatest length of time is the sanatorium physician. He has closely guided the patient's progress. A unity of opinion should be sought between him and the clinic doctor, so that the rehabilitation agencies can receive advice that will permit the continuation and guidance of the program after discharge to proceed smoothly.

To indicate to any doctor or rehabilitation agency the point the patient has reached in controlled work tolerance, standards should be brought into alignment and used throughout the country, and an activity classification such as that used at the Otisville Sanatorium (activities 0 to 8) might be suitable.

Discharge information and referal to a rehabilitation agency should be purely on the basis of physical condition. A patient may have signed out against advice or been discharged for disciplinary reasons, but the physical condition may have been excellent and the patient on much activity.

Constant and close attention by the rehabilitation agencies is as important in proper follow-up for the vocational therapy begun in the sanatorium as are the periodic examinations by the physician after discharge, to determine the progress of the patient in relation to the medical or surgical treatment in the institution. In this way only can the sanatorium recommendations be evaluated, continued or modified. The rehabilitation worker and the doctor must coöperate closely to make this essential teamwork successful. After-care should be provided for all patients whether on part-time or full-time activity or on a permanent sheltered basis. Good rehabilitation and proper after-care should definitely diminish the percentage of readmissions to tuberculosis institutions.

General: This program requires an adequate personnel. Thus, we have utilized not only our regular sanatorium maintenance divisions and employees but outside teachers for photography, stenography and typewriting and correspondence courses instead of other instructors. Recently, we appointed a full-time Director of Education to assist in the coördination and administration of the program.

Correspondence school courses should not be given unless medical indications point to a good prognosis with hospitalization required for at least three months. Furthermore, all study material, a quiet suitable place for work and close stimulating supervision should be available.

For practical training, patients will be given assignments in offices, shops and wards. These placements should be purely for their rehabilitation value and not to diminish the load of the regular employees. Patients should not be depended upon for necessary routine hospital work.

On the other hand, there are desirable services of the various departments in the program available to the institution. These include printing, mimeographing, painting, bookbinding, preparation of lantern slides and photography.

Many municipalities provide institutions for the homeless and indigent. These institutions usually utilize a good deal of inmate labor. The work of these individuals would be suitable for discharged tuberculous patients, as the job placements would include the rehabilitation assignments of the patients in the sanatorium, such as clerks, typists, carpenters' helpers, telephone operators, attendants, printers, librarians, *etc.* These transfers would solve the problem of maintenance for these patients by welfare and relief departments in the city and provide an opportunity for improvement of the patient's physical condition with continuation of rehabilitation work that could be gradually increased under proper medical observation. By the time of discharge from the welfare institution, the patients would be ready for part- or full-time outside work. State rehabilitation bureaus and other welfare and placement agencies would then be able to assign them much more easily. Arrangements have been completed for the referal of our indigent patients to Camp LaGuardia, the institution of the Welfare Department of the City of New York for homeless men. It is too early, however, for us to describe our experience with this plan.

CONCLUSIONS

1. It is our firm belief that vocational therapy is an essential routine function of the sanatorium in the treatment of tuberculosis.

2. There are numerous mental and physical benefits from this therapy. It promotes the happiness and contentment of the patient and, as ergotherapy, it is a necessary part of cure in the improvement of the patient's physical condition.

3. Vocational therapy also helps the return of the patients to industry, and thereby enables them to reach, at an early date, a satisfactory economic condition or trains them to receive educational teaching or instruction in rehabilitation units or sheltered workshops outside, and it provides information for improved household management.

4. We present a practical working program to provide this therapy on an

individual patient basis. The assignment should have a definite relationship to the patient's future occupational needs.

5. Coöperation and understanding of the personnel and patients is very essential and education is an important method in its procurement. The vocational conferences in themselves act as an educational medium.

6. This program can be made to work without prohibitive expense by utilizing the jobs inherent in the regular sanatorium administrative set-up.

7. Rehabilitation is not a medical hazard.

8. Rehabilitation follow-up is as important as medical after-care.

9. There is urgent need for a plan to accept patients on a part-time work basis after discharge for training or employment.

10. Vocational therapy can diminish the percentage of relapses and readmissions.

CONCLUSIONES

1. Proclámase la firme convicción de que la terapéutica vocacional constituye una esencial función sistemática del sanatorio en el tratamiento de la tuberculosis.

2. Esta terapéutica produce numerosos beneficios físicos y mentales, pues fomenta la dicha y contento del enfermo, y en forma de ergoterapia, constituye una parte necesaria del tratamiento dedicado a mejorar el estado físico del enfermo.

3. La terapéutica vocacional también ayuda a devolver a los enfermos a la industria, capacitándolos para alcanzar en una fecha temprana un estado económico satisfactorio, o preparándolos para recibir enseñanza o adiestramiento en las unidades de rehabilitación o en talleres *ad hoc*, y les facilita información para mejorar las tareas domésticas.

4. Preséntase aquí un plan práctico de trabajo para ofrecer esa terapéutica tomando por base las necesidades de cada individuo. La colocación del enfermo debe guardar una relación bien definida con sus futuras necesidades en cuanto a ocupación.

5. La cooperación y comprensión del personal y de los enfermos son muy esenciales, y la educación ofrece una vía importante para obtenerlas. Las conferencias vocacionales en sí mismas actúan como medio educativo.

6. Puede ponerse en operación este plan sin gastos extraordinarios, utilizando los puestos que haya vacantes en la organización administrativa del mismo sanatorio.

7. La rehabilitación no constituye un riesgo médico.

8. La observación subsecuente del resultado de la rehabilitación es tan importante como el posttratamiento.

9. Necesítase con urgencia un plan para aceptar enfermos a base de trabajo por parte del tiempo, después de darlos de alta para adiestramiento o empleo.

10. La terapéutica vocacional puede disminuir el porcentaje de recidivas y de reingresos.

We are very happy to acknowledge the financial help and personal interest of the New York, Brooklyn, and Queensboro Tuberculosis and Health Associations in their support of this program.

ANORECTAL SURGERY IN THE TUBERCULOUS[1,2]

JOSEPH GOORWITCH

Between January, 1937 and September, 1940 there were 162 patients with pulmonary tuberculosis and surgically treated anorectal disease at Olive View Sanatorium.

SEX AND AGE

Statistics of several large general hospitals located in different parts of the world are quoted in the literature as showing a greater incidence of all types of anal fistulae in males than in females; the reported percentage in males is from 60 per cent of all simple fistulae to 93 per cent of all tuberculous fistulae. At Olive View Sanatorium where females constitute slightly more than half of the patient population, 67 per cent of the entire series and 71 per cent of the "fistula" subgroup were males. No satisfactory explanation of this is available unless it is the inferior quality of anal hygiene associated with the presence of hair about the anus in males or the greater disinclination to submit to an examination on the part of females.

It is generally agreed that in tuberculous patients the age incidence of anorectal lesions corresponds to that of pulmonary tuberculosis, that is, the greatest incidence is in the third and fourth decades of life. In our entire series of 162 patients, as well as in the "fistula" subgroup of 88 patients, 69 per cent belonged to this age group; 23 per cent were over forty years of age and 8 per cent under twenty-one years. In patients under twenty-one years the incidence of anorectal disease was disproportionately low suggesting that children and youths are less prone to develop anorectal disease. The lower and upper age limits in fistula are given in the literature as fifteen and sixty-five, respectively; in the Olive View Sanatorium "fistula" subgroup these were thirteen and sixty, respectively.

It is recognized that classification of patients according to the extent of pulmonary involvement alone, although convenient, must necessarily be inadequate due to the fact that wide variations in degree of physical disability as well as resistance to tuberculosis exist. The majority of patients in our series had mixed exudative and proliferative type of tuberculosis with cavitation.

All but 3 patients, or 2 per cent, of the entire series of 162 patients had pulmonary tuberculosis; 4 patients, or 3 per cent, were classified as minimal; 40 patients, or 24 per cent, as moderately advanced; and 115 patients, or 71 per cent, as far advanced. Thus the number of far advanced patients was three times as great as that of moderately advanced in contrast to the 2:1 ratio of far advanced to moderately advanced for the entire sanatorium, suggesting that the incidence of anorectal disease increases with extent of pulmonary involvement.

[1] From Olive View Sanatorium, Olive View, California.

[2] Preliminary report read in part at a meeting of the Los Angeles Trudeau Society, May 28, 1940.

Among tuberculous patients subjected to fistulectomy the ratio of far advanced to moderately advanced is reported in the literature as ranging between 5:1 and 10:1 (21, 23, 38, 35). In our "fistula" subgroup of 88 patients the ratio is 3:1, representing a greater proportion of less advanced cases.

The incidence of positive sputum in tuberculous patients subjected to fistulectomy as reported in the literature is from 50 per cent to 95 per cent (3, 31, 39, 40, 21, 23). In our "fistula" subgroup the incidence of positive sputum was 80 per cent, as compared to 67 per cent for the entire series of 162 patients and about 50 per cent for the population of the entire sanatorium, suggesting that inflammatory anorectal lesions might be caused, or maintained, or both by tubercle bacilli.

OTHER EXTRAPULMONARY TUBERCULOSIS

The larynx was involved in 14 per cent of the entire Olive View series. Bronchoscopy was employed only when tuberculous tracheobronchitis was suspected or major chest surgery contemplated; of 51 patients bronchoscoped, 35 per cent were found to have tuberculous involvement. X-ray examination of the gastrointestinal tract was likewise employed only when indicated and a small number of patients was subjected to proctoscopy or laparotomy; 13 per cent of 24 patients thus examined were found to have intestinal tuberculosis or tuberculosis of the appendix.

ANORECTAL DISEASE

The great majority of reports on anorectal disease in tuberculous patients deals with lesions of the "fistula" type which includes abscesses, sinuses and fistulae. Simple cryptitis is said to be very common and this was substantiated by findings at Olive View Sanatorium.

In the majority of our patients more than one anorectal lesion was found at the initial examination, with a total of 255 lesions in 162 patients.

As shown in table 1 the incidence of anorectal lesions is greater among patients with anorectal symptoms than among those examined routinely on admission. The Olive View series consists of surgically treated patients only which explains the higher incidence of lesions when compared to the other series given in table 1.

Haemorrhoids and fissures: In the Olive View series of internal-external haemorrhoids and fissures the sex distribution, National Tuberculosis Association classification and sputum status vary but little as compared to those of the entire series studied. This suggests that sex, extent of pulmonary involvement and sputum status bear no particular relationship to the incidence of haemorrhoids and fissures, except for the universally greater incidence of all anorectal disease in males.

One hundred and ten patients, or 68 per cent, had internal-external haemorrhoids, and of these, 45 per cent also had a sinus or fistula.

Forty-two patients, or 27 per cent, had a total of 47 anal fissures. Practically all fissures were associated with other lesions, 77 per cent of these being haemor-

rhoids; 70 per cent of anal fissures occurred at 6 o'clock, that is, in the posterior commissure; sex apparently did not favor any particular location of fissures. Anatomical factors in the pathogenesis of anal fissures as presented by Blaisdell (5) seem to offer an explanation for the great predominance of fissures in the posterior commissure and for the satisfactory results obtained by the division of the subcutaneous fibres of the external sphincter.

TABLE 1

Anorectal lesions in sanatorium tuberculosis patients

LESIONS	AUTHOR, DATE, NUMBER AND TYPE OF PATIENTS AND INCIDENCE OF LESIONS			
	Fansler & Petter, 1931, 138 ♂ examined on admission	Marino *et al.*, 1938, 227 ♂ examined on admission	C. L. Martin, 1939, 88 pts., with symptoms	Goorwitch, 1941, 162 pts., 67% ♂, with symptoms
Hemorrhoids	94 (68%)	128 (56%)	32 (36%)	110 (68%)
Fissures	13 (10%)	24 (10%)	11 (12%)	47 (39%)
"Fistulae"	14 (10%)	36 (15%)	18 (20%)	96 (58%)
Total	189	276	88	255

TABLE 2

Sex, National Tuberculosis Association classification and sputum status in the "fistula" subgroup

Sex	Male	62 (71%)
	Female	26 (29%)
N. T. A. Classification	Nontuberculous	2 (2%)
	Minimal and moderately advanced	22 (25%)
	Far advanced	64 (73%)
Sputum status	Positive	69 (80%)
	Negative	19 (20%)
Total		88 (100%)

Incidence of anal "fistulae": Under the term of "fistulae" are included related lesions such as perianal and ischiorectal abscesses, sinuses and fistulae of the anocutaneous, anovaginal and other types.

Forty-nine patients, or 30 per cent of all patients and 58 per cent of the "fistula" subgroup, presented evidence of unhealed operative anorectal wounds when first seen at the Olive View Sanatorium Proctologic Clinic. Table 2 shows a greater proportion of males and incidence of positive sputum in the "fistula" subgroup than in the entire series studied.

A total of 96 lesions was found in the "fistula" subgroup: abscesses 14 (15 per cent), submucous sinuses 9 (9 per cent), sinuses 8 (8 per cent), and fistulae 65 (68 per cent). In the small group of abscesses only 14 per cent were char-

acteristically "cold." The great majority of fistulae were of the anocutaneous type, 61; there were 3 anovaginal and one rectovesical fistulae.

The most frequent location of the internal opening in fistulae was at 6 o'clock, 46 per cent, with 12 o'clock a close second, 25 per cent. In the majority of cases in which the internal opening was not identified on examination of crypts it was found with the aid of injection of dilute aqueous solution of methylene blue; less often it was identified by the presence of a thickening in the crypt involved.

The incidence of anal "fistulae" of whatever cause has been reported in the literature as less than 1 per cent of all admissions to large general hospitals. In very large series of proctologic cases anorectal "fistulae" are reported to constitute 5 to 30 per cent. The incidence of tuberculous "fistulae" was reported by early German workers as 50 per cent of all anorectal "fistulae," the diagnostic criterion being the coexistence of pulmonary tuberculosis. Work done during the last two decades, mostly in the United States and some in England, revealed an incidence of tuberculous "fistulae" of 3 to 20 per cent of all "fistulae," depending on diagnostic criteria, sex and source of material. The diagnostic criteria varied from coexisting extra-anorectal tuberculosis to demonstration of tubercle bacilli or tuberculous changes by bacteriological or histological examination of tissue or secretions.

The incidence of "fistulae" in tuberculous patients in the United States has been reported as 0.8 to 11.7 per cent. At Olive View Sanatorium a rough estimate would be 3 per cent, at least for the period included in this study.

The incidence of tuberculous "fistulae" among tuberculous patients varies from 0.33 per cent (20) to 11.7 per cent (38), the wide range of incidence again being due to differences in diagnostic criteria. The question "What percentage of all 'fistulae' in the tuberculous are tuberculous" is discussed in a number of papers on the subject; 56 to 90 per cent of all "fistulae" in the tuberculous have been reported as tuberculous. In recent years, however, the consensus has favored the tuberculous nature of practically all "fistulae" in the tuberculous, and that this could be proved bacteriologically and histologically. Table 3 demonstrates that in our series 39 per cent of 64 "fistulae" in which a single section was examined histologically revealed characteristic evidence of tuberculous involvement, the remaining 61 per cent showing only chronic granulation tissue which might or might not be due to tuberculosis. There are two factors which probably tended to lower the frequency of histological diagnosis of tuberculosis: making a single section only and partial destruction of tissue by electrocautery used in fistulectomies. The incidence of positive sputum in those diagnosed tuberculous and in those not diagnosed tuberculous was 88 per cent in the former and 82 per cent in the latter.

PATHOGENESIS OF TUBERCULOUS "FISTULAE"

It is generally thought that infection leading to abscess and later fistula originates in a crypt and burrows its way into perianal tissues; at this starting point is located the internal opening of the tract for which Buie (11) suggests

the more appropriate term of primary opening. According to Bochner, ischiorectal abscesses fail to heal spontaneously because of the anatomically noncollapsible nature of the fossa, therefore incision alone does not result in cure, excision is necessary (7).

That in tuberculous patients the original lesion in the bowel wall is caused by the tubercle bacillus and is later invaded by the pyogens to form an abscess may be nothing more than a conjecture (20). On the other hand, in tuberculous patients the abscess caused by pyogens may be secondarily invaded by the tubercle bacillus giving rise to the chronic, poorly healing fistula known as tuberculous. True tuberculous perianal abscesses, so-called "cold" abscesses, are not common. In the small series of 14 abscesses in our study, only 2 were of the "cold" variety. Of course, the mere presence of pyogens does not necessarily exclude the tubercle bacillus from being the primary aetiological agent in the formation of a "hot" abscess, but actual evidence to support this view is lacking.

TABLE 3

*Histological findings in "fistula" subgroup**

HISTOLOGICAL FINDINGS	INCIDENCE
Tuberculous granulation tissue (areas of necrosis consistent with tuberculosis)	7 (11%)
Tubercles and giant cells	18 (28%)
Chronic granulation tissue	39 (61%)
Total	64 (100%)

* Emil Bogen, M.D., Olive View, California, Pathologist.

Tuberculous fistulae are said to be caused and maintained by the tubercle bacillus (20). That in tuberculous patients fistulae of whatever aetiology are maintained in their chronicity by the tubercle bacillus, in the presence of inadequate drainage, is suggested by histopathological findings; this would justify the inclusion, under the term tuberculous, of any fistula maintained in its chronicity by the tubercle bacillus regardless of the primary aetiological agent.

It is stated that it is impossible to determine the frequency of superinfection of an ordinary abscess by tubercle bacilli, thus converting it into a tuberculous lesion, yet the conclusion is drawn that viable and virulent tubercle bacilli are the primary aetiological agent in anal abscess or fistula simply because in tuberculous patients tubercle bacilli are frequently found in the terminal bowel (39, 40, 41). Obviously tuberculous anal lesions in tuberculous patients may not be diagnosed bacteriologically due to contamination by tubercle bacilli from the terminal bowel, a fact not yet generally recognized (42).

It is generally admitted that anorectal tuberculosis is secondary to tuberculosis elsewhere, usually pulmonary or intestinal or both. That primary anorectal tuberculosis, that is, one without the presence of extra-anorectal tuberculosis, is rare, if at all found, seems to be the opinion of the majority of the writers on the subject in recent years. The extreme of this opinion is illustrated by Spies-

man's rule "No pulmonary tuberculosis—no anorectal tuberculosis" (53). At Olive View Sanatorium where practically all patients are admitted with a diagnosis of pulmonary tuberculosis the problem of primary anorectal tuberculosis is not encountered.

DIAGNOSTIC CRITERIA OF TUBERCULOUS "FISTULAE"

In recent years diagnostic criteria of tuberculous "fistulae" varied all the way from the gross appearance of the lesion through coexisting pulmonary tuberculosis and recovery of tubercle bacilli by bacteriological examination of secretions or tissue from anorectal lesions down to demonstration of typical tuberculous changes by histological examination of serial sections of tissue. It is logical to assume that, as Sweany put it, with proper "sampling" of tissue and serial sections the great majority of fistulae in tuberculous individuals can be proved to be tuberculous by the only reliable diagnostic method, the histological examination.

Does recovery of tubercle bacilli by bacteriological methods from an anorectal lesion of a tuberculous individual prove that the lesion is tuberculous? Many writers (3, 13, 38, 45, 46) answer in the affirmative. An opposing view is presented on the basis of finding a high percentage of tuberculous patients harboring viable and virulent tubercle bacilli in the terminal bowel; the conclusion is drawn that culture and animal inoculation methods are of little value in tuberculous patients in establishing the tubercle bacillus as the aetiological agent of anorectal lesions in contrast to the real value of histopathological examination (39, 42). There is no more reason for answering the question in the affirmative than there is for stating that recovery of tubercle bacilli by bacteriological methods from tonsil or appendix tissue in a tuberculous patient makes a diagnosis of tuberculosis of tonsil or appendix, respectively, without further examination.

Does recovery of tubercle bacilli or demonstration of histological changes of tuberculosis in fistulous tissue of a tuberculous patient prove that the tubercle bacillus was the primary aetiological agent of the anal lesion? This question was answered in the affirmative on the basis of finding a high incidence of tubercle bacilli by bacteriological methods of examination in fistulous tissue of patients who had pulmonary tuberculosis and failure to recover tubercle bacilli in fistulous tissue of patients free of pulmonary tuberculosis (13). The significance of these findings seems to lie in the demonstration that the terminal bowel of nontuberculous individuals is free of viable and virulent tubercle bacilli whereas that of tuberculous patients is not (40, 42), and also that primary anorectal tuberculosis is rare, if found at all. Unless an abscess is typically "cold" or unmixed or histological evidence of tuberculosis is obtained in the very earliest stage of the gross lesion its original aetiology may be uncertain.

In apparently nontuberculous patients the value of recovery of tubercle bacilli from anal lesions by any method, provided the organisms are viable and virulent, is obvious in so far as directing attention to the probability of the primary focus being extra-anorectal, most often in the respiratory or digestive system or both. However, as almost all agree that treatment of tuberculous "fistulae" should differ from that of nontuberculous only in greater thoroughness of ex-

cision of involved tissue, the question of diagnosis is relatively unimportant as far as the anorectal lesion itself is concerned.

TREATMENT

Review of available literature shows that caudal and parasacral or lumbar anaesthesia was the method of choice; only a single preference for general anaesthesia because of postoperative difficulties of spinal anaesthesia was encountered (7). In the Olive View series of 162 patients treated surgically[3] no difficulties were encountered which would make lumbar anaesthesia unsuitable. For fissurectomy, abscess drainage and nonextensive second and multiple stage fistulectomy, infiltration anaesthesia with 1 per cent procaine hydrochloride solution has been employed.

Only few authors recommend placing the patient for operation in the prone position with pelvis elevated; in our series the lithotomy position was the usual one and only occasionally was Sims' position employed.

Dissection-ligature-excision was the method employed in haemorrhoidectomies. Fissurectomy was accomplished by Gabriel's method of excision of an inverted V-shaped section of adjacent skin and sharp division of the fibres of the subcutaneous sphincter; the fissure bed was often cauterized.

There is general agreement that perianal abscesses should be drained as soon as discovered, although a few workers (45, 46, 47) recommend waiting for fluctuation. The technique usually employed in draining perianal abscesses is complete unroofing of the external wall followed by fistulectomy as chronicity of the lesion is established.

Survey of the literature reveals that in fistulectomy both sharp dissection and electrocauterization are employed widely. The proponents of the cautery method state that it eradicated tuberculosis whereas the knife spread it (20, 21, 22, 23, 13). Without giving statistical data, gratifying results were claimed with the use of sharp dissection thus avoiding the "sloughing, ugly and slow healing wounds" resulting from the employment of electrocautery (38). In the Olive View series the Bovie electrosurgical unit was used almost exclusively in first-stage fistulectomies and was found satisfactory. As shown in table 4 the multiple stage group consisted of 10 patients on whom a total of 39 fistulectomy stages was performed; about half of these were very minor procedures carried out under infiltration anaesthesia for the purpose of improving drainage but which were nevertheless classified as operative stages. Whatever technique is employed, radical excision of involved tissue must be carried out if cure is to be expected; few authors in recent years recommended mere opening of fistulous tracts followed by cauterization.

The use of methylene blue in the identification of sinuses and tracts has not been mentioned very often in the literature but, where mentioned, the more frequent recommendation was not to employ it. In our series it was found to be useful. Prolonged packing of wounds or their suture is not recommended in

[3] Dr. Robert L. Belt, Montrose, California, Consultant in Proctology.

recent literature as their harm is obvious in prevention of good scar formation and subsequent predisposition to incontinence; in this connection Blaisdell's excellent presentation of the surgical anatomy of the anal sphincter mechanism is most illuminating (6).

In the postoperative care of anal wounds, cleanliness, daily dressings and prevention of bridging to insure healing from the bottom up are recognized as essential. At Sea View Hospital fistulectomy wounds are loosely packed with codliver oil dressings and the results are reported as satisfactory (30, 32). It

TABLE 4

Operations and stages

OPERATION	..STAGES ON.. PATIENTS	EXPLANATIONS
Haemorrhoidectomy	96	41 alone 28 with fistulectomy 27 with fissurectomy
Fissurectomy	42	8 alone 7 with fistulectomy 27 with haemorrhoidectomy
Drainage of abscess	10	Preliminary to fistulectomy
Repair of sphincter	2	
Excision of infected pilonidal cyst	1	
Fistulectomy	146 on 88	51 one-stage operations on 49 patients 56 (54 two-stage operations on 27 patients; 2 first-stage operations on 2 patients) 39 three stages and more on 10 patients
Total	297 on 162 patients at 235 sittings	

was recommended that following anorectal surgery tuberculous patients stay in bed at least four weeks as compared to four days for nontuberculous patients (20, 21, 23). In our series such a degree of conservatism has not been practiced and in a maximum of one week the patients were permitted to resume their preoperative activities; many of the patients were strict bed patients prior as well as following surgery.

OPERATIVE RESULTS AND RATE OF HEALING

The follow-up in our series is as of January, 1941.

All 96 patients subjected to haemorrhoidectomy achieved complete healing

in from one-half to two months. The average healing time in the group of patients subjected to haemorrhoidectomy alone or to haemorrhoidectomy and fissurectomy was one month regardless of their sputum status.

TABLE 5

Operative results in fistulectomy

AUTHOR AND YEAR	HOSPITAL AND TYPE	PATIENTS WITH PULMONARY TUBERCULOSIS AND ANAL FISTULA	OPERATIVE TECHNIQUE (MOSTLY SPINAL ANAESTHESIA)	OPERATIVE RESULTS IN PER CENT	
				healed	
Fansler and Petter 1927	Sanatorium and private practice	40	Cautery	85	15 died unhealed
Fansler and Petter 1931	Sanatorium and private practice	78	Cautery	90	10 died unhealed
Martin 1933	Chicago Municipal Sanitarium	75	Sharp dissection	87	13 died unhealed
Berry 1934	Bellevue (Tuberculosis)	18	Sharp dissection	72	28 unhealed
Chisholm and Gauss 1935	Denver Sanatorium and private practice	71	Cautery	98	2 unhealed
Granet and Gerendasy 1939	Sea View Hospital (tuberculosis)	50	?	70	10 died unhealed, 20 living unhealed
Buie, Smith and Jackman 1939	Private practice	32	?	100	
Joynt 1940	Queen Alexandra Sanatorium (Canada)	61	?	76	14 died unhealed, 10 living unhealed
Granet 1940	Sea View Hospital (tuberculosis)	100	Cautery discarded in favor of knife	74	12 died unhealed, 14 living unhealed
Goorwitch 1941	Olive View Sanatorium	88	Cautery (predominantly)	81*	4 died unhealed, 15 living unhealed

* Inasmuch as 2 patients had only first-stage fistulectomy because they failed to return for completion of surgery, the true incidence of healing is 83 per cent.

Of the 42 patients subjected to fissurectomy 39, or 93 per cent, achieved complete healing in an average of one and three-fourths months. The 3 patients who failed to achieve healing in from five to twenty-nine months were all far advanced with positive sputum and also unhealed fistulectomy wounds.

As shown in table 5 healing of fistulectomy wounds has been reported in the literature rather consistently by those who presented statistical data along with

their conclusions. In contrast to this are the somewhat older statements that in the few patients in whom fistulectomy succeeds in producing healing the pulmonary process is likely to become progressive, whereas as long as the fistula is allowed to discharge the pulmonary disease remains quiescent (25, 45). In our "fistula" subgroup of 88 patients the mortality rate calculated on the basis of patient-years was 6 per cent as compared with an intramural mortality of about 5 per cent for the sanatorium as a whole.

One and one-half to four months were given as the average length of time consumed in healing of fistulectomy wounds in the tuberculous (13, 38, 10, 39, 40, 41). In evaluating the data of our series it must be kept in mind that various diagnostic and therapeutic procedures carried out for the extra-anorectal disease often were responsible for delay between successive stages of fistulectomy and failure to attend the Proctologic Clinic which in turn resulted in artificial increase in the length of time consumed in healing.

It has been claimed that tuberculous fistulectomy wounds healed slower than nontuberculous ones (10, 48) and that in sputum-negative tuberculous patients healing was as good as and as rapid as in non-tuberculous individuals (average of one and one-half months), whereas patients with positive sputum took twice as long to heal (38). In our series no relationship was observed between the rate of healing and sputum status; the average rate of healing was identical in the sputum-positive and sputum-negative groups. The conclusion drawn from these findings is that adequate drainage and satisfactory reparative power are of greater importance than the extent of pulmonary involvement and the sputum status. The rôle of satisfactory drainage in the rate of healing is further emphasized by the 100 per cent healing in the group of haemorrhoidectomies regardless of the sputum status.

In the one-stage fistulectomy group of 49 patients 44, or 90 per cent, achieved complete healing in an average of two and one-fourth months. The remaining 5 patients, or 10 per cent, failed to achieve healing in an average of nine months. In the two-stage fistulectomy group of 29 patients, 27 patients had both stages completed and 2 had only the first stage done because they failed to return for completion of surgery. Of the 27 patients, 21 patients, or 78 per cent, achieved complete healing in an average of four and one-half months from the date of the first stage. The remaining 6 patients, or 22 per cent, failed to achieve complete healing in an average of eight months. Inasmuch as 78 per cent of patients in the one-stage fistulectomy group and 70 per cent of patients in the two-stage group had positive sputum at the time of operation and 49 per cent and 41 per cent respectively at the time of discharge, and yet the incidence of healing in the groups was 90 per cent and 78 per cent respectively, positive sputum cannot be regarded as the only factor responsible for failure to achieve wound healing in 100 per cent of cases.

In the multiple-stage fistulectomy group of 10 patients who had a total of 39 operative stages, 6 patients, or 60 per cent, achieved complete healing in an average of ten months and the remaining 4 failed to heal in an average of twenty-three months from the date of the first stage. Of the 10 patients in this group

90 per cent were males, 80 per cent had far advanced pulmonary tuberculosis and all had positive sputum at the time of operation. Of the 4 patients who remained unhealed, 2 achieved sputum conversion, one is classified as arrested, one as quiescent, one as improved and one as unimproved. Failure of these patients to achieve healing is attributed to either very extensive lesions or lesions of long standing or both.

Included in the fistulectomy group are 3 cases of anovaginal fistulae, 2 of which healed following a two- and a three-stage fistulectomy, respectively, and the third patient left prior to complete healing. One case of rectovesical fistula took three years to heal and that only after operative intervention for unilateral renal tuberculosis and nephrolithiasis in the presence of vesical tuberculosis.

COMBINED OPERATIVE RESULTS

Of the 162 patients in the entire series who were subjected to 297 operative procedures at 235 sittings, 145 patients, or 90 per cent, achieved complete healing and 17, or 10 per cent, failed to heal completely. In the "fistula" subgroup of 88 patients, 71 patients, or 81 per cent, achieved complete healing and of these, 6 are dead (8 per cent mortality); the remaining 17 patients, or 19 per cent, failed to achieve healing and of these, 4 are dead (24 per cent mortality); the mortality for the entire "fistula" subgroup was 11 per cent.

The 145 patients who achieved healing have been observed at Olive View Sanatorium for one to thirty-eight months (average of ten months) following complete healing. Of this group, 34 patients are still at the sanatorium; for the remaining patients the period of observation ended at the time of discharge so that with the exception of the 14 patients who are dead the actual number of months since the date of complete healing is much greater than the average of ten months given above.

POSTOPERATIVE COMPLICATIONS

No aggravation of pulmonary disease that could be attributed to anaesthesia or operation was observed. In several instances operation was done at the patient's request and in the presence of unmistakable evidence of downward progress and hopeless prognosis. Postoperative complications were divided into two groups: those obviously due to operation and those questionably due to operation. To the former group belong 4 patients with the following complications: 2 haemorrhages, one following fistulectomy by sharp dissection and the other by electrocautery; one temporary, partial incontinence following fistulectomy in a patient with an extensive fistula draining for fifteen years; and one temporary but prolonged and complete incontinence in a patient admitted to Olive View Sanatorium with a fibrosed anal canal and gas incontinence following fistulectomy one year prior to admission. To the group of complications questionably due to operation belong two: a perianal abscess developing one month following fistulectomy and an anal fistula one month following haemorrhoidectomy.

STATUS OF PATIENTS IN JANUARY, 1941

For those who survived to date the change in extent of pulmonary involvement is slightly toward improvement, that is, there is a slight increase in the number of patients classified as moderately advanced and a decrease in the number of far advanced. The status as of January, 1941 is as follows: arrested or apparently arrested 23 per cent, quiescent 22 per cent, improved 38 per cent, unimproved 8 per cent and dead 9 per cent. Calculated on the basis of patient-years the mortality rate was 5.3 per cent. The change in the sputum findings as compared with those at the time of operation are as follows: absence of expectoration three times as great, incidence of negative sputum twice as great, and of positive sputum about half as great.

In the group of 17 patients (including the 2 patients who left Olive View Sanatorium following first-stage fistulectomy and prior to completion of surgery) who failed to achieve healing, 84 per cent had positive sputum at the time of operation and 59 per cent in January, 1941 or at the time of discharge or death. All 17 patients had unhealed, or rather only partially healed, fistulectomy wounds; 82 per cent were classified as far advanced; 40 per cent of the 15 patients who had histological examination of fistulous tissue presented evidence of tuberculosis. The status of these patients as of January, 1941 is as follows: 9 are improved or better, 4 are unimproved and 4 are dead. Thus as a whole this group of 17 patients had more extensive pulmonary involvement and was in poorer general condition (24 per cent mortality) than the entire "fistula" subgroup (11 per cent mortality), in spite of the fact that the incidence of positive sputum at the time of operation and at the time of discharge was only slightly higher than in the entire "fistula" subgroup.

In the group of 14 dead patients all were classified as far advanced and all had positive sputum at the time of operation and most of them also at the time of death. The average age at the time of death was thirty-seven years and the postoperative survival was from three to twenty-two months, an average of one year. All but one died of progressing tuberculosis. Among the 4 patients whose anorectal wounds were only partially healed at the time of death the operation was fistulectomy in one and fistulectomy and fissurectomy in 3. Of the remaining 10 patients whose wounds had healed, the operation was haemorrhoidectomy in 3, haemorrhoidectomy and fissurectomy in one, haemorrhoidectomy and fistulectomy in one, and fistulectomy in 5. A finding worth noting is the fact that of the 11 dead patients in whom histological examination of tissue was done only one revealed definite evidence of tuberculosis and this patient achieved complete healing of the fistulectomy wound in three months and died of progressing pulmonary and laryngeal tuberculosis one year later at the age of fifty-six.

INDICATIONS AND CONTRAINDICATIONS IN ANORECTAL SURGERY

Practically all recent writers on the subject agree that on the whole tuberculous patients make good surgical risks for proctological operations under lumbar

or caudal anaesthesia, and that elimination of a suppurative focus such as an anal fistula contributes to the patient's well-being. Despite this practical unanimity of opinion various indications and contraindications to surgery are given. Thus it was claimed that the gross appearance of the fistulous lesion reflects on the status of pulmonary disease and on ultimate prognosis, that lack of scar tissue in a fistulous lesion is usually accompanied by lack of fibrosis of pulmonary lesions; accordingly it was recommended that the treatment of anorectal lesions should depend on the patient's resistance to the tubercle bacillus and that, if pulmonary disease was not healing, the chances were that the reparative powers of an operative wound would be low (22). It was also recommended that anal fistulae should not be operated on in the presence of active pulmonary tuberculosis because wounds rarely heal and there is an increase of pulmonary disease (45, 46). It seems to be probable that patients who are subjected to fistulectomy prior to diagnosis of pulmonary tuberculosis and who grow worse following operation do so not because of the operation *per se* but because they were not treated for pulmonary tuberculosis when first seen.

Opposed to these views is that holding that pulmonary activity is no objection to surgery, in fact, cleaning up of a rectal condition reflected favorably on the pulmonary state (13, 30, 52). Other workers recommend that the optimum time for surgical interference is when the sputum is negative or the bacillary count is low; although the great majority of anorectal wounds did heal, the rate of healing in the presence of positive sputum was only half as great as in its absence (38). Accordingly these authors advise against operating for nontuberculous anorectal lesions in patients with active pulmonary tuberculosis and positive sputum for fear that these wounds may become tuberculous (30, 32, 38). In the Olive View patients in whom haemorrhoidectomy was not accompanied by fistulectomy and in whom the incidence of positive sputum was about 50 per cent, all healed and the average rate of healing was one month, both in the sputum-positive and the sputum-negative patients.

In the Olive View series no observations were made regarding any relationship between fibrosis in anorectal lesions and in pulmonary lesions; however, the fact that 71 per cent of those who died had healed wounds, whereas 41 per cent of those alive but with unhealed wounds have pulmonary lesions of the mixed type and negative sputum, suggests that the course of pulmonary lesions and the sputum status are not intimately related to the reparative abilities of the patient as far as anorectal wounds are concerned. Mortality rates calculated on the basis of patient-years in our series do not indicate any detrimental effect of anorectal surgery, and especially fistulectomy, on the course of pulmonary disease. For the entire Olive View series the mortality rate was 5.3 per cent and for the "fistula" subgroup 6 per cent which compares not unfavorably with the intramural mortality of about 5 per cent for the entire sanatorium population, calculated on patient-year basis.

SUMMARY AND CONCLUSIONS

1. A comparative study is presented comprising experience in proctologic surgery at Olive View Sanatorium between January, 1937 and September, 1940 with a follow-up as of January, 1941 and a review of available literature, mostly American, on the subject of anorectal disease in the tuberculous.

2. A total of 225 anorectal lesions, excluding cryptitis, were found in the Olive View Sanatorium series of 162 patients who had anorectal symptoms. The 10 to 15 per cent incidence of fistula, as reported in the literature, in tuberculous males examined on admission makes such a plan of routine anorectal examination on admission worth the effort.

3. There is no actual evidence to support the view that the primary aetiological agent of perianal abscesses in tuberculous patients is the tubercle bacillus. Because tubercle bacilli are commonly found in the terminal colon of tuberculous patients, their recovery from the contents of perianal abscesses cannot be regarded as evidence of their rôle as primary aetiological agent. As a perianal abscess in a tuberculous patient goes on to formation of a chronic fistula only histological evidence of tuberculosis should be regarded as diagnostic. A tuberculous anorectal fistula is defined as one caused or maintained by the tubercle bacillus as determined by adequate histological examination of pathological tissue. Inasmuch as primary anorectal tuberculosis is probably nonexistent the demonstration of tubercle bacilli by improved bacteriological examination of abscess contents (47) or fistulous tissue is of value only in apparently nontuberculous patients, in which cases investigation for the presence of tuberculosis in the respiratory and digestive systems is in order.

4. A total of 297 operative procedures at 235 sittings were carried out on the Olive View Sanatorium series of 162 patients; 90 per cent of these achieved healing and 9 per cent died, a patient-year mortality of 5.3 per cent. The operative results for haemorrhoidectomy were healing in 100 per cent and for fissurectomy in 93 per cent. In the Olive View Sanatorium fistula subgroup of 88 patients, 83 per cent achieved complete healing and 4 per cent died unhealed. In this series no relationship has been observed between rate of healing and sputum status.

SUMARIO Y CONCLUSIONES

1. Preséntase un estudio comparado que comprende las observaciones en cirugía proctológica realizadas en el Sanatorio Olive View de enero 1937 a septiembre 1940, con observación subsecuente hasta enero de 1941, y un repaso de la literatura disponible, principalmente en Estados Unidos, acerca de la afección anorrectal en los tuberculosos.

2. En la serie de 162 enfermos del Sanatorio Olive View que tenían síntomas anorrectales, se descubrieron 225 lesiones anorrectales, excluída la criptitis. El coeficiente de 10 a 15 por ciento de fistula en los tuberculosos varones examinados a su ingreso que se menciona en la literatura, demuestra que vale la pena establecer un plan semejante de examen anorrectal sistemático al ingreso.

3. No hay datos que apoyen la opinión de que el bacilo tuberculoso sea el agente etiológico primario de los abscesos perianales en los tuberculosos. Dado que se encuentran habitualmente bacilos tuberculosos en la porción terminal del colon de los tuberculosos, no puede considerarse su aislamiento en el contenido de los abscesos perianales como prueba de su papel etiológico primario. Visto que un absceso perianal en un tuberculoso prosigue hasta formar una fístula crónica, los únicos signos que deben aceptarse como diagnósticos de tuberculosis son los histológicos. Cabe definir como fístula anorrectal tuberculosa la provocada o mantenida por el bacilo tuberculoso, determinado esto mediante un adecuado examen histológico del tejido patológico.

4. En la serie de 162 enfermos del Sanatorio Olive View se llevaron a cabo 297 intervenciones cruentas en 235 sesiones; 90 por ciento de los enfermos curaron y 9 por ciento murieron, o sea una mortalidad de 5.3 por ciento por enfermo-año. Los resultados operatorios con la hemorroidectomía fueron: curación en 100 por ciento y con la fisurectomía en 93 por ciento. En el subgrupo de 88 enfermos con fístula del Sanatorio Olive View, curaron completamente 83 por ciento, y 4 por ciento murieron sin curar. En esta serie no se observó relación alguna entre la velocidad de la curación y el estado del esputo.

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TUBERCULOSIS OF THE EAR AND MASTOID IN ADULTS

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Tuberculosis involving the middle ear and mastoid was recognized clinically and pathologically many years before the tubercle bacillus was identified as the causative agent. Reports by Schwartze (1, 2), von Trölsch (3), Toynbee (4), Zaufal (5), Wilde (6), Politzer (7, 8) were among the earliest to describe the symptoms and course of the chronic otorrhoea frequently found in patients with chronic pulmonary tuberculosis. Eschle (9), in 1883, was apparently the first investigator to isolate tubercle bacilli from aural discharge. The early history of tuberculosis involving the middle ear and mastoid, as well as complete bibliographies, have been published by Milligan (10), Grimmer (11) and Miller (12).

From January 1, 1924 to January 1, 1941, we have observed 140 adults in whom a diagnosis of tuberculous otitis media was made. Table 1 shows the frequency of tuberculous otitis media in the patients admitted to Glen Lake Sanatorium during the period of study.

There are 83 males and 57 females in the group studied.

The condition was unilateral in 124 (right 70, left 54) and bilateral in 16 (11.43 per cent), making a total of 156 involved tympani.

The age distribution of the patients studied is shown in table 2. It will be noted in the table that the patients with bilateral involvement are included twice and the age of onset of each is considered separately. Three patients with unilateral disease were eliminated because the tuberculosis seemed to be superimposed on a chronic otitis media present since childhood. The table, therefore, shows the age incidence of 121 unilateral and 16 bilateral cases making a total of 153 involved tympani. The youngest patient included was fourteen years of age and the oldest sixty-eight years. Adults thirty years of age or less comprise over 50 per cent of the entire group.

RELATION TO PULMONARY AND EXTRAPULMONARY TUBERCULOSIS

Table 1 shows that 138 patients had active pulmonary tuberculosis and only 2 patients had extrapulmonary tuberculosis without active pulmonary tuberculosis. One hundred and sixteen (84.1 per cent) had far advanced pulmonary tuberculosis, 21 (15.2 per cent) moderately advanced and one (0.7 per cent) minimal. The classification used is the one recommended by the National Tuberculosis Association. Pulmonary cavitation was present in 130 (94.2 per cent). In 134 (97.1 per cent) tubercle bacilli were demonstrated in the sputum, either by direct examinations or by guinea pig inoculations. These figures confirm the statement made repeatedly that tuberculous otitis media

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occurs most commonly in patients having advanced pulmonary tuberculosis. In 62 patients the disease has terminated fatally, 57 have been discharged alive and in the majority of these the pulmonary lesion was considered arrested. Twenty-one are still under treatment.

As mentioned previously, 2 patients did not have an associated active pulmonary tuberculosis. One of these had Pott's disease and tuberculous cervical adenitis. The other had tuberculosis involving the elbow, knee, spine, peritoneum and cervical lymph nodes. In the remaining 138 patients, 77 (55.8 per cent) had other extrapulmonary tuberculous foci. The intestine, larynx, cervical lymph nodes, kidney, rectum, bones and joints were the organs most frequently involved in the order named.

TABLE 1

Incidence of tuberculosis of the ear in patients admitted to Glen Lake Sanatorium January 1, 1924 to January 1, 1941

STAGE OF PULMONARY TUBERCULOSIS	NUMBER	TUBERCULOSIS OF EAR	PER CENT
Far advanced	2,972	116	3.90
Moderately advanced	1,459	21	1.44
Minimal	435	1	0.23
Total	4,866	138	2.84
Extrapulmonary tuberculosis without active pulmonary tuberculosis	293	2	0.68

TABLE 2

*Age distribution of patients with tuberculous ears**

	AGE GROUPS						
	14–20	21–30	31–40	41–50	51–60	61–69	TOTAL
Number	14	65	33	27	9	5	153
Per cent	9.1	42.5	21.6	17.6	5.9	3.3	100.0

* Reason for apparent discrepancy in numbers explained in text.

It is apparent, therefore, that tuberculous otitis media is a local manifestation of a serious constitutional disease and this fact must be recognized when treating tuberculosis of the middle ear.

DIAGNOSIS

The diagnosis is dependent upon the history, the presence of other tuberculous foci, the examination of the ear, the finding of tubercle bacilli in the aural discharge and the examination of any tissue removed from the middle ear or the mastoid.

The history is typical in most of these patients. The first subjective symptom is usually a sense of fulness in the affected ear with a rapidly developing loss of hearing. Buzzing, ringing, throbbing, humming or crackling frequently follow

and pulsations are not uncommon. These symptoms are followed by aural discharge starting a few days to a few weeks after the onset of the early symptoms. The discharge is serous and scant but rapidly becomes purulent and may be profuse. In some cases the first discharge is thick and cheesy in character. Pain is usually absent or slight and the absence of pain is important for diagnosis. However, it may be well to point out that moderate pain was noted by 26 patients, while severe pain was complained of by 4. The presence of pain does not entirely eliminate tuberculosis. The pain, when present, is most marked just prior to the rupture of the drum and the beginning of the discharge. In occasional cases the early symptoms are absent or not mentioned and the presence of discharge is the first symptom noted. In this series the otitis media was always secondary to tuberculosis elsewhere in the body.

The appearance of the tympanic membrane depends upon the stage of the disease at the time of the examination. In 45 patients we were able to observe the earliest changes and follow them to the development of the perforation and discharge. Inflammation usually involving Shrapnel's membrane and extending inferiorly along the handle of the malleus was the earliest change noted. This inflammatory reaction increases rapidly so that in a few days the entire tympanum is inflamed and oedematous. In some cases, just prior to the development of the perforation, a yellowish centre forms, and it is through this area that the drum perforates. The perforation is small at first but may increase in size gradually or rapidly until a large portion of the drum may eventually be destroyed. Often, however, the perforation remains small throughout the entire course. Multiple perforations have been described by Bruck (13), Grimmer, Milligan, Ormerud (14) and others as characteristic of tuberculosis. Souper (15), Muskat (16), and Miller, on the other hand, have rarely observed multiple perforations. In our series 3 drums with 2 perforations each were observed and in one drum 4 perforations were noted. In the remaining involved drums only single perforations of varying sizes were seen. Granulations are frequently present and occasionally are abundant. In one patient they grew to such size that they completely obstructed the external auditory canal. The granulations are polypoid and fleshy in appearance and bleed easily when traumatized.

Hearing tests reveal a moderately severe deafness usually of the obstructive type. Tests used include the watch, whispered voice, spoken voice, Weber, Rinne, and in some cases audiometer studies.

Whenever secretion is available for study, search is made for the tubercle bacillus. Inoculation of the discharge into guinea pigs is the most accurate method of diagnosis. In 144 draining ears where such examination was made, 122 (84.7 per cent) were proved tuberculous by this method. We do not consider smears satisfactory as they have not proved accurate in our hands. In 35 patients smears and guinea pig inoculations were made concomitantly and in 18 no tubercle bacilli were found by smear where the guinea pig tests subsequently revealed tuberculosis. In one patient, tubercle bacilli were found by smear but the guinea pig test failed to confirm their presence. It is desirable to search for the tubercle bacilli as soon as possible after the discharge develops

as they are more easily found at this time. When the discharge is chronic, tubercle bacilli may be difficult to find because of the overgrowth of secondary organisms. Wingrave (17) has pointed out that the finding of acid-fast bacilli by smear is not sufficient to identify tubercle bacilli and their pathogenicity should be proved by guinea pig inoculation. Therefore, we have discontinued using smears routinely for identification of tubercle bacilli.

Our present technique is to collect some of the discharge with a sterile applicator which is placed in a sterile tube containing 4 cc. of physiological saline solution. This is centrifuged and at least 1 cc. of the mixture is injected intraperitoneally into a guinea pig. The pig is sacrificed at the end of six weeks and the organs are studied for evidence of tuberculosis. We formerly made four injections a week apart into the same guinea pig but are now making only a single injection. Our results have been satisfactory with this technique.

Any tissue obtained from the middle ear or mastoid is examined microscopically or the material is ground up, suspended in physiological saline solution and injected into a guinea pig. One patient had large granulomata removed on four occasions and each time tubercles were demonstrated microscopically. In another patient material obtained from the mastoid at the time of operation was examined for the presence of tubercle bacilli but none were found. However, pus from an abscess, which formed in the operative wound, contained tubercle bacilli.

RELATION TO MASTOID

With the exception of one patient, in whom a facial paralysis developed, there was no clinical evidence suggesting involvement of the mastoid process unless one considers a chronic discharge from the middle ear as evidence of a chronic mastoiditis. Roentgenological studies of the mastoid process revealed involvement in 90 of 92 patients with unilateral disease so studied. In 13 patients with bilateral tuberculous otitis media, 11 showed bilateral involvement of the mastoids roentgenographically, while in 2 other patients unilateral involvement could be demonstrated. Changes observed ranged from diffuse cloudiness of the mastoid cells seen early to extensive bone destruction usually observed late. The early changes were noted at the time of the earliest otitic symptoms or very shortly thereafter. Tuberculous mastoiditis could not be differentiated from any other inflammatory reaction in the mastoid. The roentgenological changes persisted regardless of the subsequent course of the disease.

Tuberculosis involving the petrosal portion of the temporal bone was found in 10 patients at postmortem examination. We have so far been unable to demonstrate the tuberculous petrositis even when special roentgenographic studies were made.

ROUTE OF INFECTION

Most investigators believe that the tubercle bacilli reach the middle ear by way of the eustachian tube. As pointed out by Fraser (18), the eustachian tube itself may or may not be involved. In adults, relatively few cases result from

a blood-borne infection. We have not observed the extension of a tuberculous lesion in the external auditory canal to the tympanum and the middle ear. The spread of a tuberculous lesion from the throat to the ear is possible but cannot be proved. In 14 patients tonsillectomy was performed and in 10 tubercles were demonstrated microscopically. This could well be a coincidental finding as latent tuberculosis of the tonsils is found frequently in the presence of advanced pulmonary tuberculosis.

We believe that sputum infected with tubercle bacilli precipitated the otitis media in the majority of the cases. It is significant that a pulmonary haemorrhage antedated the otitis media by three to five weeks in 45 patients. Surgery appeared to be the precipitating factor in 5 cases, 4 occurring shortly after a thoracoplasty and one, apparently haematogenous, followed the removal of a tuberculous appendix.

COMPLICATIONS

The complications of tuberculous ears most commonly reported are meningitis, labyrinthitis, facial paralysis and cerebral abscess. These complications have been reported frequently in the literature but usually the studies were concerned with children. In our series 2 patients developed miliary tuberculosis with meningitis but the pulmonary tuberculosis probably was the source of the haematogenous spread. Only one patient developed a facial paralysis. Mild vertigo was present occasionally but serious labyrinthitis was not observed. Two patients developed tuberculous abscesses of the temporal lobe. Excluding mastoiditis, serious complications of tuberculous otitis media in adults are uncommon in our experience.

TREATMENT

Tuberculosis of the middle ear is always a complication of tuberculosis elsewhere in the body and therefore adequate treatment of the pulmonary and extrapulmonary tuberculosis is extremely important. This, of course, is best carried out in a sanatorium.

The ear is kept as dry as possible by frequent wiping and dry wicks are left in the ear and changed as often as necessary if the discharge is profuse. Heliotherapy is applied locally by means of the Kromayer (water cooled mercury-quartz) lamp and a special ear applicator. Exposure of five seconds daily is given at the start and gradually increased to ten seconds. The ear should be wiped dry before the lamp treatment is given. The value of local heliotherapy is questionable.

We have insufflated a powder consisting of 25 per cent potassium iodide in boric acid and feel it has been extremely helpful in reducing the amount of the discharge. In many cases this powder has been an important factor in the healing of the tuberculous otitis media. The ear is first carefully wiped dry and the powder is insufflated once or twice a week through a DeVilbiss powder blower.

Recently, Muskat (19) has advocated the routine eradication of the mastoid process in all patients with tuberculous otitis media. We do not believe such

a procedure is indicated routinely. Certain conditions should be fulfilled before a radical mastoid operation is recommended. The patient should demonstrate the ability to control his tuberculosis, at least partially, regardless of the location of the tuberculous lesion. In other words, since we have no adequate measure of a patient's resistance, the patient himself must demonstrate that resistance. The advanced pulmonary case with an acute, progressive tuberculosis and a poor or hopeless prognosis should not be subjected to any surgery, except as an emergency may arise. Since conservative treatment will heal over 50 per cent of cases with middle ear tuberculosis, it seems only fair to give that treatment a reasonable trial first. Mastoid surgery should at least be limited, in adults, to those patients in whom the pulmonary lesion is either partially or completely controlled and where the ear continues to discharge an appreciable amount in spite of adequate local and general treatment.

Myerson and Gilbert (20) list the following indications for radical mastoid surgery in tuberculous mastoiditis: subperiosteal abscess, circumscribed labyrinthitis, facial paralysis, persistent postauricular fistula after simple mastoidectomy, mastoid tenderness and headache associated with profuse discharge.

The patient should use a back rest instead of lying in the recumbent position when he has a pulmonary haemorrhage; this upright position may prevent infected blood from reaching the middle ear and avoid the development of tuberculosis.

Myringotomy is not advised in the acute congestive stage unless severe pain is present.

Granulations may be cauterized with 25 per cent silver nitrate or removed surgically if overly abundant.

RESULTS OF TREATMENT

Our records were complete enough to determine the results of treatment in 132 patients with 148 infected tympani. Eight were eliminated for statistical purposes because of incomplete records. The findings are tabulated in table 3. We included in the classification of apparently healed those patients who developed a perforation with aural discharge and in whom the ear subsequently became dry and remained dry for a period of at least six months. The perforation may or may not have healed. Ten (6.8 per cent) patients did not have a perforation or aural discharge and healed their infection with scarring of the tympanum and deafness as the end result. In the unhealed patients the ear continued to drain up to the time they were discharged from the sanatorium or they are still under treatment. If there was any aural secretion the ear was not considered healed. The difference in the results of treatment in the patients who were discharged as dead when compared with those who were discharged alive or still under treatment is particularly striking. Approximately 80 per cent of the two latter groups are either apparently healed or healed as compared with only 27.4 per cent in the former group. The poor results in the patients with progressive and fatal tuberculosis are due probably to their loss of resistance. Tuberculosis of the ear is often a terminal manifestation and many of the patients

with progressive tuberculosis received little or no treatment because their condition was poor and their prognosis was hopeless. Our results demonstrate the relationship between general resistance to tuberculosis and the beneficial results of treatment.

It is well to point out, however, that the ear apparently healed in some patients in spite of the fact that the general condition steadily grew worse and death ensued. In other patients the otitis media developed while the pulmonary lesion was improving and the ear continued to discharge and did not heal, even though the pulmonary tuberculosis apparently was controlled.

TABLE 3

Results of treatment of 148 tuberculous ears, exclusive of 8 where the end result is unknown

DISPOSTION OF CASE	NUMBER	APPARENTLY HEALED		NO PERFORATION HEALED		UNHEALED	
		Number	Per cent	Number	Per cent	Number	Per cent
Still under treatment	24	16	66.7	2	8.3	6	25.0
Discharged dead	62	14	22.6	3	4.8	45	72.6
Discharged alive	62	46	74.2	5	8.1	11	17.7
Total	148	76	51.4	10	6.8	62	41.8

PROGNOSIS

Death was caused or hastened appreciably in 2 patients by the development of a tuberculous cerebral abscess. In the 2 patients who developed a tuberculous meningitis there was also a chronic pulmonary tuberculosis with bilateral cavitation and a superimposed generalized miliary tuberculosis. It is probable that the meningitis was secondary to the miliary spread from the pulmonary tuberculosis.

The hearing in the affected ear is diminished early in the course of the disease, and this is one of the earliest symptoms. The degree of loss of hearing seems to be out of proportion to the extent of drum involvement observed when the case is seen early. The loss of hearing is usually permanent. There is no recovery of fine hearing, although occasionally there is some improvement in the gross hearing, especially if the ear becomes dry.

The discharge in most cases is chronic and may persist in spite of treatment and despite complete control of the pulmonary lesion. In 34 patients observed from incipiency to complete healing the duration of the discharge averaged 309 days, ranging from 7 days to 1,085 days.

The perforation in the tympanic membrane is usually permanent. In occasional cases, where the original perforation remains small, the defect may close.

Relapse after apparent healing occurs occasionally but responds readily to further treatment.

SUMMARY AND CONCLUSIONS

1. Tuberculosis of the middle ear in adults is usually a chronic disease, characterized clinically by acute onset, absence of severe pain, chronic discharge, severe permanent hearing loss and absence of fatal complications due to the ear condition.

2. There is rarely any clinical evidence of temporal bone involvement although roentgen examination of the mastoid shows early and persistent changes in nearly every case.

3. In this series the ear condition was always secondary to tuberculosis elsewhere in the body and was most often associated with advanced pulmonary tuberculosis, pulmonary cavitation and positive sputum.

4. The disease is usually caused by sputum or blood, infected with tubercle bacilli, reaching the middle ear through the eustachian tube. Haematogenous infection is less common in adults but occurs.

5. Tuberculosis of the middle ear may be expected in about 3 per cent of patients with advanced pulmonary tuberculosis.

6. A tentative diagnosis may be made from the history of onset, the presence of tuberculosis elsewhere in the body and the examination of the ear.

7. The diagnosis may be confirmed by the inoculation of aural discharge into a guinea pig. This is the most reliable single diagnostic aid. We have succeeded in recovering tubercle bacilli in more than 80 per cent of suspected tuberculous otitis media when discharge was available for examination.

8. The treatment consists of sanatorium care, control of the pulmonary lesions, local cleansing, local heliotherapy, 25 per cent potassium iodide in boric acid used as an antiseptic powder and radical mastoid surgery in specially indicated cases.

9. Complete healing apparently takes place in more than half of the cases and is, to a large degree, dependent upon the general resistance of the patient to tuberculosis.

10. In a few cases complete healing will occur without perforation of the tympanum or any demonstrable discharge. The diagnosis in these cases is based on clinical observation.

11. Tuberculosis of the middle ear is a serious disease only as it affects the hearing. It does not, however, usually affect the prognosis of the patient as far as it concerns life expectancy.

SUMARIO Y CONCLUSIONES

1. La tuberculosis del oído medio en los adultos suele ser una afección crónica, caracterizada clínicamente por iniciación aguda, falta de dolor intenso, supuración crónica, pérdida permanente y grave de la audición, y falta de complicaciones letales debidas al estado otítico.

2. Rara vez hay el menor signo clínico de invasión del temporal, aunque el examen roentgenológico del seno mastoideo revela en casi todos los casos alteraciones tempranas y persistentes.

3. En esta serie el estado auditivo fué siempre secundario a tuberculosis de otra parte del cuerpo, y más a menudo asociado con tuberculosis pulmonar avanzada, cavernas pulmonares y esputo positivo.

4. La enfermedad suele ser ocasionada por la llegada de esputo o sangre infectada al oído medio a través de la trompa de Eustaquio. La infección hematógena es menos frecuente en los adultos, pero también se presenta.

5. Puede esperarse encontrar tuberculosis del oído medio aproximadamente en 3 por ciento de los casos de tuberculosis pulmonar avanzada.

6. Puede hacerse un diagnóstico tentativo guiándose por la historia de la iniciación, la presencia de tuberculosis en otra parte del cuerpo, y el examen del oído.

7. Puede confirmarse el diagnóstico mediante la inoculación de la secreción auditiva en el cobayo, lo cual constituye el más fidedigno auxiliar aislado en el diagnóstico. En más de 80 por ciento de casos sospechosos de otitis media tuberculosa se encontraron bacilos cuando había exudado para examen.

8. El tratamiento consiste en la asistencia sanatorial, cohibición de las lesiones pulmonares, limpieza local, helioterapia local, aplicación, como polvo antiséptico, de yoduro de potasio al 25 por ciento en ácido bórico, y cirugía mastoidea radical en los casos indicados especialmente.

9. La curación completa aparentemente tiene lugar en más de la mitad de los casos, y en gran parte depende de la resistencia general del enfermo a la tuberculosis.

10. En algunos casos de obtendrá la curación completa sin perforación del tímpano o supuración observable. El diagnóstico en estos casos se basa en al observación clínica.

11. La tuberculosis del oído medio es una afección grave únicamente en lo tocante a la audición. Sin embargo, no suele afectar el pronóstico en lo que se refiere a la expectativa de vida.

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PUTRID LUNG ABSCESS TREATED WITH CONTINUOUS TRANSTHORACIC ASPIRATION (MONALDI METHOD)[1]

RALPH ROSENBLOOM AND ALBERT GUGGENHEIM

The treatment of putrid lung abscess has been mainly directed toward the establishment and maintenance of adequate drainage of pus. Various investigators (Maxwell (1) Rosenblatt (2), Viswanathan (3) and others) have suggested a period of conservative management to precede attempts at active intervention. On the other hand, Neuhoff and his coworkers (4) and Overholt and Rumel (5) favor the institution of early surgical drainage. The favorable results obtained with the various surgical methods suggest that the purely conservative treatment be deferred in favor of early active surgical intervention.

In certain cases, however, even relatively small surgical procedures may involve too great a risk. The possibility of treating lung abscess by continuous aspiration has been suggested by one of us (6). In 10 patients with tuberculous cavities this procedure which was inaugurated by Monaldi (7) in 1938 has been used at the National Jewish Hospital since 1939. With the initial successes in tuberculous cavities in mind a case of putrid nontuberculous lung abscess was treated with the same technique which was described by us in a previous publication (6). In reviewing the literature we have been unable to find any reference concerning the use of the so-called "Monaldi method" for nontuberculous cavities.

REPORT OF CASE

R. P., white male, was admitted to the National Jewish Hospital on June 21, 1940 at the age of thirty-eight. He gave a history of the usual childhood diseases, parotitis in 1927, paranasal sinusitis since 1928; cough and expectoration since 1920. Patient had had several haemoptyses in 1929 and 1930.

In March, 1940 patient contracted a severe illness characterized by pain in his right chest, chills, dyspnoea, increased cough and expectoration. Pneumonia and pleural effusion on the right were diagnosed. Two attempts to aspirate the right pleural cavity were unsuccessful.

On admission the patient was acutely ill in a state of emaciation and prostration. His temperature was 102°F., pulse weak, 124 per minute, respirations 28 per minute. The patient expectorated about 300 cc. of putrid pus daily which was negative for tubercle bacilli on 40 subsequent direct smears, one culture, 2 guinea pig inoculations. The tuberculin reaction was positive with 1 mg. Cultures for pyogenic organisms revealed aerobic and anaerobic gram-negative cocci in clusters, diplococci and bacilli.

Physical examination showed the right hemithorax fixed with respiration. There was dulness over the entire posterior and upper half of the anterior right chest. The breath sounds were bronchovesicular anteriorly and diminished posteriorly. There were moist râles over the upper half of the right chest anteriorly. X-ray examination of the chest on June 22, 1940 showed a large circumscribed area of homogeneous density over the

[1] From the Medical Department of the National Jewish Hospital, Dr. Charles J. Kaufman, Medical Director, Denver, Colorado.

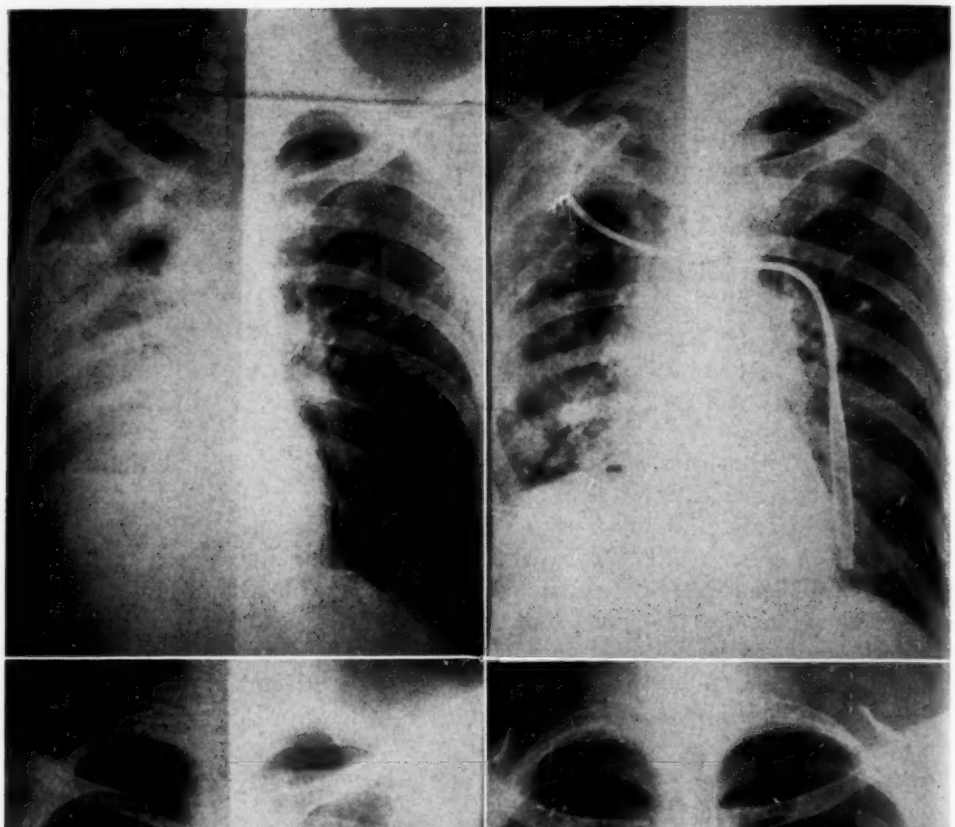

FIG. 1. (Upper left.) X-ray taken after bronchoscopic drainage shows a large abscess cavity with fluid level occupying the upper third of the right lung.

FIG. 2. (Upper right.) Six weeks after aspiration was started. Abscess with catheter *in situ* appears considerably smaller.

FIG. 3. (Lower left.) One month after removal of the catheter, there is no evidence of an abscess.

FIG. 4. (Lower right.) Bronchogram with iodochloral (July 2, 1941) reveals evidence of bronchoectasis in right middle and lower lobe.

right upper third. There was extensive radio-opacity in the right lower two-thirds suggesting pneumonic consolidation and pleural effusion.

Three hundred and fifty cc. of putrid pus were aspirated from the pleural cavity. Bacteriological examination of the pus revealed aerobic and anaerobic gram-positive and negative cocci. Fungus cultures remained sterile.

The patient's condition grew rapidly worse. Resection of portions of the fifth rib posteriorly and thoracotomy were performed and 1,000 cc. of pus were evacuated. The density in the right upper lobe persisted, suggesting an intrapulmonary location of the lesion. The suspicion of a bronchopleural fistula was confirmed by expectoration of methylene blue which had been instilled into the right pleural cavity.

On August 3, 1940 a bronchoscopy was performed and a large amount of putrid material issuing from the right upper lobe bronchus was aspirated. Post-bronchoscopic X-ray examination showed a large abscess-cavity in the region of the previously present density (figure 1). Patient's condition improved temporarily. On August 13, 1940 more adequate drainage of the empyema was obtained by resection of a portion of the ninth rib posteriorly.

The patient's condition was still extremely poor, the large abscess-cavity persisted and active intervention was indicated. Because extensive surgical procedures were considered too dangerous, it was thought that continuous transthoracic aspiration of the abscess might be applicable in this case. The chest was explored and it was found that the pleural layers were adherent infraclavicularly. On August 24, 1940 a catheter was inserted under local anaesthesia into the abscess-cavity through the first anterior intercostal space. Intracavitary water-manometer readings were +4, −4. On the next day continuous aspiration was started by means of a water pump with an average negative pressure of 10 cm. of water and maintained day and night. The amount of pus aspirated during the first few days averaged about 80 cc. in twenty-four hours. The sputum, which already had decreased after the thoracotomies, dropped to 60 cc. and lost its foul odor. The amount of material aspirated decreased rapidly and after four weeks neither pus nor air were being discharged through the catheter. Suction was discontinued but the catheter was left in place (figure 2). The catheter was slowly expelled spontaneously and on November 18, 1940 (eighty-five days after induction) it was removed. The sinus tract closed within a few days. An X-ray film taken shortly afterwards showed the abscess completely healed (figure 3).

After introduction of the catheter the patient's condition improved rapidly. The empyema cavity became smaller and the bronchopleural fistula was not demonstrable any more. A small tube is maintained in the pleural cavity but discharge has ceased. Pus and sputum were consistently negative for tubercle bacilli.

Bronchograms with lipiodol revealed the presence of bronchiectatic changes in both lower lobes and in the right middle lobe (figure 4). Daily amount of sputum is 20 cc. X-ray films of the paranasal sinuses were normal.

The patient is in excellent condition and has been put on increasing exercise. He has gained 40 pounds in weight.

DISCUSSION

There is no doubt that in this case no surgical risk was involved by the use of continuous aspiration and that the procedure may be considered as fully successful. Prerequisites for this treatment are the roentgenological visibility and the accessibility of the abscess and the obliteration of the pleural space in

the region where the abscess is entered. In our case, although a free pleural space existed posteriorly forming the empyema cavity, at the site of entry into the abscess anteriorly it was found to be obliterated. The intrapulmonary location of the abscess was confirmed by intracavitary manometric readings and by the fact that pus was evacuated by bronchoscopy. During the course of continuous aspiration a bronchopleural fistula closed; its presence had been proven by the expectoration of dye instilled into the pleural cavity.

We were not able to establish the identity of the aerobic and anaerobic organisms which were cultured from sputum and pleural pus; the absence of their pathogenicity was proven by animal inoculation. No tubercle bacilli were found. We feel that there was a pathogenic relationship in this case between lung abscess and bronchiectasis.

Various explanations can be given for the rapid closure of the abscess after continuous aspiration had been started. The maintenance of negative pressure within the abscess cavity over a prolonged period of time caused diminution in the size of its lumen and the reëxpansion of surrounding lung tissue. At the same time air was aspirated from the draining bronchi through the abscess; the oxygen in this air may have destroyed the anaerobic organisms. The air passing through the abscess may have had the same effect as zinc peroxide, as used by Overholt and Rumel for the liberation of oxygen. It was noted that in the latter part of aspiration no air escaped any longer through the catheter. This suggests that the draining bronchi closed in the course of aspiration.

SUMMARY AND CONCLUSION

A patient with putrid lung abscess, complicated by a bronchopleural fistula, putrid empyema and bronchiectasis, was treated by continuous transthoracic aspiration of the abscess cavity. This method was used because more extensive surgical procedures represented too great a risk. The technique employed was the same as that used in continuous aspiration (Monaldi method) of tuberculous cavities. The result obtained was surprisingly satisfactory. The method may warrant further consideration in the treatment of certain cases of putrid lung abscess.

SUMARIO Y CONCLUSIONES

Un enfermo con un absceso pulmonar pútrido, complicado con fístula broncopleural, empiema pútrido y bronquiectasia, fué tratado por la aspiración transtorácica continua del absceso. Se empleó este método porque las intervenciones quirúrgicas más extensas entrañaban un riesgo exagerado. La técnica empleada fué la misma utilizada para la aspiración continua (método de Monaldi) de las cavernas tuberculosas. El resultado obtenido sorprendió por lo satisfactorio. Vale la pena considerar la misma técnica en el tratamiento de ciertos casos de absceso pulmonar pútrido.

We wish to acknowledge our thanks to Dr. Merrill C. Jobe who performed the rib resections and to Dr. Herman I. Laff who performed the bronchoscopy.

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RETENTION OF TUBERCLE BACILLI BY THE KIDNEY OF THE RABBIT[1]

Study II

DIRAN YEGIAN AND JOSEPH M. KURUNG

There is a striking difference between the response of the kidney of the guinea pig and that of the rabbit to infection with the tubercle bacillus. The lesions of the kidney, with rare exceptions, are microscopical in the guinea pig and gross and wide-spread in the rabbit. This contrast in the extent of the disease might be attributed to the fact that tubercle bacilli deposited in the kidney are more quickly eliminated by the guinea pig than by the rabbit.

Yegian (1) found that in normal and sensitized guinea pigs, tubercle bacilli appear in the urine in from eight to fifty minutes following the intravenous injection of the bacilli. An important feature of the experiment was the avoidance of instrumentation in the collection of the urine. Urination was spontaneous or induced by gentle pressure over the region of the bladder.

The present study deals with the elimination of tubercle bacilli by the kidney of the rabbit. The literature, here briefly reviewed, shows a disparity of opinion on the subject. Tsuge (2) injected rabbits intravenously with 0.02 mg. of human tubercle bacilli. Five minutes after the intravenous injection, the urine, collected by catheter, was free from red blood cells and contained tubercle bacilli. Lieberthal and von Huth (3) injected a number of rabbits intravenously with a suspension of tubercle bacilli. Twenty-four hour specimens of urine, collected over a period of twenty days in metabolism cages, were cultured and found negative for tubercle bacilli. Wyler (4) injected bovine tubercle bacilli into the renal artery of rabbits and collected urine by catheter over a period of three days. The urine specimens, examined by smears, culture and guinea pig inoculation were found negative for tubercle bacilli.

PROCEDURE

Young cultures of human tubercle bacilli, strain H37, cultivated on Long's synthetic medium, were suspended in salt solution. Five cc. of the suspension (50 mg.) were injected into the exposed right jugular vein of the animal. Each rabbit, just previous to the intravenous injection, was fed 75 cc. of water to increase the flow of urine. The animal was then placed in a cone, caudal end protruding, and maintained in this position until urination occurred spontaneously, or was induced at the end of one hour by the exercise of gentle pressure over the region of the bladder. The specimen of urine was collected in a sterile receptacle.

The first experiment included 20 six months old rabbits, each weighing approximately 2,000 g.; 15 of the animals were healthy and the remaining 5 had been sensitized by the injection into the groin of a heavy suspension of

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

attenuated tubercle bacilli, strain R1.[2] Fourteen of the animals in this group were sacrificed immediately after the specimen of urine was collected. The organs on gross examination were natural in appearance. On microscopical examination, no lesions were found in the kidney, but acid-fast microörganisms were widely scattered throughout the organ. The remaining 6 animals were sacrificed two months after the intravenous injection of the bacilli, and at necropsy there was gross evidence of tuberculosis in the kidneys.

The specimen of urine from each of the 20 rabbits (15 healthy and 5 sensitized) was obtained in from ten to seventy-five minutes following the intravenous injection of tubercle bacilli. Urination in most instances was induced, and the amount of urine collected varied from 4 to 15 cc. The specimen of urine collected from each of the 20 rabbits was examined microscopically for the presence of red blood cells and acid-fast microörganisms. None were found. There was added to each specimen of urine an equal amount of a 4 per cent solution of sodium hydroxide. The urine was incubated for thirty minutes, neutralized with hydrochloric acid, centrifuged and the residual 3 cc. injected intraperitoneally into a healthy guinea pig. The 20 guinea pigs so injected were sacrificed ten weeks later, and in no instance was evidence of tuberculosis found.

The above experiment indicates that in healthy and sensitized rabbits, tubercle bacilli do not appear in the urine in from ten to seventy-five minutes following an intravenous injection of large numbers of tubercle bacilli.

The purpose of the second experiment was to determine the lapse of time between the intravenous injection of the bacilli and the appearance of these microorganisms in the urine. The experiment comprised 8 six months old rabbits, each weighing approximately 2,000 g. Four of the animals were healthy and 4 had been previously sensitized by an injection into the groin of 50 mg. of attenuated tubercle bacilli, strain R1. The same procedure was adopted as in the preceding experiment. The results of the experiment are shown in table 1. On the first, fourth and sixth days following the intravenous injection, the microscopical examination and the cultivation of the urine of the 8 rabbits in this group failed to reveal tubercle bacilli. On the eighth day, however, acid-fast microörganisms were found for the first time on microscopical examination in 3 of the 8 specimens of urine, and tubercle bacilli were demonstrated in the urine of all 8 rabbits on cultivation and on animal inoculation. Four of the animals (2 healthy and 2 sensitized) were sacrificed on the eighth day and stained microscopical sections of the kidneys of the 4 animals showed areas of tubercle formation with acid-fast bacilli.

On the twelfth day, specimens of urine from the 4 remaining animals (2 healthy and 2 sensitized) contained tubercle bacilli as determined by cultivation and animal inoculation. The 4 animals were sacrificed at this time, and stained preparations of the kidneys showed the presence of tubercle formation with acid-fast bacilli.

The experiment indicates that the tubercle bacillus is retained by the kidney

[2] The strain was kindly provided us by the Saranac Lake Laboratory.

TABLE 1

	RABBIT NUMBER	AMOUNT URINE COLLECTED	UNSTAINED SEDIMENT	EXAMINATION OF URINE FOR TUBERCLE BACILLI	CULTURES FOR TUBERCLE BACILLI	ANIMAL INOCULATION	KIDNEY STAINS FOR TUBERCLE BACILLI
		cc.					
1st day	45	14	Negative for blood cells	Negative	Negative		
	41	16	Negative for blood cells	Negative	Negative		
	34S*	10	Negative for blood cells	Negative	Negative		
	36S	18	Negative for blood cdlls	Negative	Negative		
	44	25	Negative for blood cells	Negative	Negative		
	40	32	Negative for blood cells	Negative	Negative		
	35S	15	Negative for blood cells	Negative	Negative		
	38S	20	Negative for blood cells	Negative	Negative		
4th day	45	15	Negative for blood cells	Negative	Negative		
	41	18	Negative for blood cells	Negative	Negative		
	34S	25	Negative for blood cells	Negative	Negative		
	36S	30	Negative for blood cells	Negative	Negative		
	44	18	Negative for blood cells	Negative	Negative		
	40	22	Negative for blood cells	Negative	Negative		
	35S	14	Negative for blood cells	Negative	Negative		
	38S	31	Negative for blood cells	Negative	Negative		
6th day	45	65	Negative for blood cells	Negative	Negative		
	41	70	Negative for blood cells	Negative	Negative		
	34S	60	Negative for blood cells	Negative	Negative		
	36S	70	Negative for blood cells	Negative	Negative		
	44	30	Negative for blood cells	Negative	Negative		
	40	60	Negative for blood cells	Negative	Negative		
	35S	15	Negative for blood cells	Negative	Negative		
	38S	45	Negative for blood cells	Negative	Negative		
8th day	45	80	Negative for blood cells	Negative	Positive	Positive	Positive
	41	150	Negative for blood cells	Negative	Positive	Positive	Positive
	34S	130	Negative for blood cells	4 acid-fast bacilli	Positive	Positive	Positive
	36S	150	Negative for blood cells	1 acid-fast bacilli	Positive	Positive	Positive
	44	130	Negative for blood cells	2 acid-fast bacilli	Positive	Positive	
	40	120	Few red blood cells	Negative	Positive	Positive	
	35S	150	Negative for red blood cells	Negative	Positive	Positive	
	38S	150	Negative for red blood cells	Negative	Positive	Positive	
12th day	44	50	Negative for red blood cells	Negative	—	Positive	Positive
	40	100	Negative for red blood cells	Negative	—	Positive	Positive
	35S	75	Negative for red blood cells	3 acid-fast bacilli	—	Positive	Positive
	38S	125	Few red blood cells	Negative	—	Positive	Positive

* Sensitized.

of the rabbit, and not until the advent of tubercle formation and cellular damage are the bacilli found in the urine.

CONCLUSIONS

Tubercle bacilli are eliminated by the normal kidney of the guinea pig, whereas in the rabbit the microörganisms are eliminated only after tubercles have developed in the kidney. To this difference in the capacity of the kidney of these two animals to eliminate tubercle bacilli, might be attributed the contrast in the extent of the tuberculous disease which these organs present at necropsy.

CONCLUSIONES

El riñón normal del cobayo elimina los bacilos tuberculosos, mientras que el del conejo sólo los elimina después que se han formado tubérculos en el órgano. A esta diferencia en la capacidad del riñón para eliminar bacilos tuberculosos puede atribuirse la diferente extensión que presenta la enfermedad tuberculosa en los órganos de estos animales en la autopsia.

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(3) LIEBERTHAL AND VON HUTH: Surg., Gynec. & Obst., 1932, *55*, 440.
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Sensitized

THE DERMATO-PULMONARY REACTION[1]

IV. Effect of Tuberculin Reaction upon the Lung

S. PUDER

In the course of our studies of the dermato-pulmonary reaction we reported in the first paper on animal experiments which showed that (*1*) pneumothorax treatment alone causes no inflammatory reaction in the lung, and (*2*) skin irritation connected with pneumothorax treatment causes an inflammatory reaction in the organ. Thus it has been proved that the dermato-pulmonary reaction does not spread by contiguity but ensues by a reflex mechanism. A direct proof of this statement was produced in the second paper in which we demonstrated the alteration of the stellate ganglion on the irritated side. Dilatation of the vessels, haemorrhages, cellular infiltration and changes of the ganglion cells were observed. The alteration corresponded to a focal ganglionitis, whereas the opposite ganglion was normal. The assumption of a reflex arc has been anatomically demonstrated by the lesion of the ganglion. In the third paper the results of acute experimental tuberculosis in rabbits were reported. It was found that more extensive and severer tuberculosis developed on the side of skin irritation (skin irritation had been applied without measuring its dose). In this paper the hope was expressed that, by measuring the doses of irritation, we may, according to Arndt-Schulz' rule on stimulus threshold, be able to apply a dose of irritation not promoting but inhibiting the tuberculous changes.

Here, the effects of tuberculin reaction on the lung are reported. Normergic, normal, noninfected and allergic rabbits were used. Allergy was induced by inoculation with bovine bacilli; six platinum loops of bacteria were suspended in 9 cc. of physiological saline solution and 0.2 cc. of the suspension were injected under the skin of the abdomen. After a thorough depilation of the chest 4 normergic and 4 allergic rabbits were given intracutaneously 0.2 cc. each of Old Tuberculin 1:1000 on the right side of the chest. Four normergic and 4 allergic rabbits were treated with undiluted tuberculin in the same manner. Of each of the above groups consisting of 4 rabbits, 2 rabbits were killed after twenty-four hours and 2 rabbits after one week. Beside these, 2 rabbits served as control animals, one of them having been depilated only and the other was rendered only allergic.

In the normergic animals it was found, especially after a treatment with concentrated tuberculin, that the right lung of the animal killed twenty-four hours after inoculation was twice as large as the left one (figure 1). It was inflated, friable, and had a dark red surface, mottled with densely scattered punctiform haemorrhages at places confluent and forming a bloody infiltration. The costal impressions were discolored over all lobes, whereas the interspaces were bulging

[1] From the Dispensary and Department of Pulmonary Tuberculosis of the National Social Insurance Institute of Hungary at Pestszenterzsebet, near Budapest.

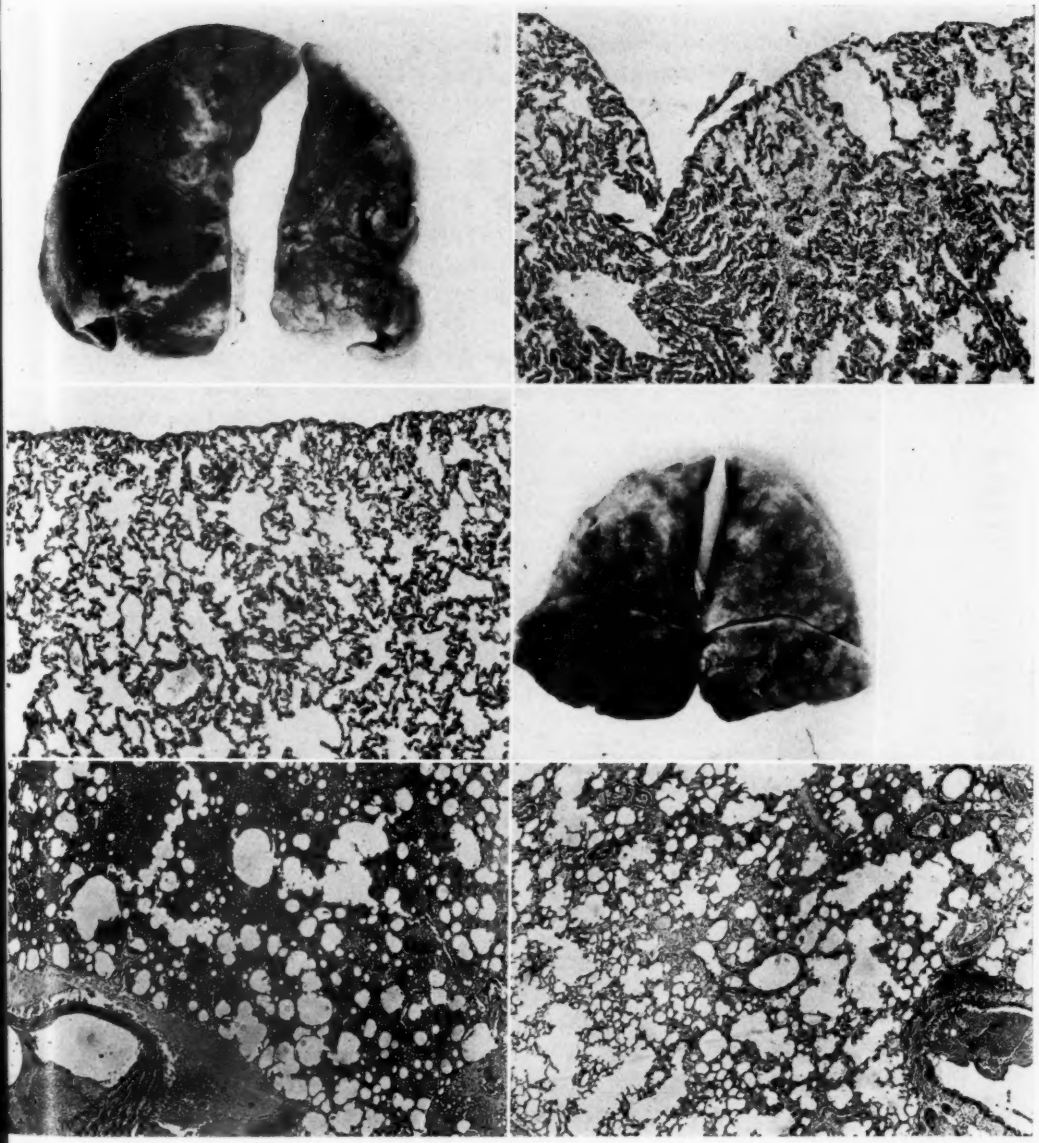

FIG. 1. (upper left.) FIG. 2. (upper right.) FIG. 3. (center left.) FIG. 4. (center right.)
FIG. 5. (bottom left.) FIG. 6. (bottom right.)

and had generally preserved the natural color of the lung. The left lung showed no alteration; it was collapsed, rosy, and spongy on touch. Microscopically there was an advanced emphysema in the right lung, with torn septa and extensive haemorrhages, involving groups of 3 to 5 alveoli. There was congestion, the vessels and bronchi were filled with blood. The left lung had a normal air content. At some places a slight emphysema and moderately dilated vessels with normal blood content could be seen. The bronchi contained blood also on this side, possibly by aspiration from the other side.

In the allergic animals, the right lung of the animals killed twenty-four hours after inoculation with diluted tuberculin showed microscopically a more marked congestion (figure 2). There was much blood in the bronchi, and subpleural ecchimoses were present. No haemorrhage could be seen in the right lung (figure 3).

The lung of the animals treated with undiluted tuberculin and killed one week later, was enlarged, dense, consolidated and, at places, gland-like on touch. The middle and inferior lobes were pitting, dark red, infiltrated by haemorrhagic spots. The left lung was pinkish (figure 4).

Microscopically there was oedema and haemorrhage filling the air vesicles throughout the right lung, the vessels were distended, the bronchi full of blood. The bronchial epithelium was detached and catarrhal phenomena were present. The alteration was gradually increasing toward the interior of the lobe. Besides, there were large periarterial serous effusions (figure 5).

In the control experiment with depilation of the chest (the animal was killed one week after depilation) there were no gross or microscopical changes in the lung (figure 6).

The other control animal was rendered allergic only and killed after two weeks. Both lungs of this rabbit were enlarged, cushion-like on touch, red, with dark red haemorrhagic infiltration at the edges, especially in the inferior lobe which had the consistency of liver. No tubercles could be seen on gross or microscopical examination.

SUMMARY

After an intracutaneous tuberculin injection on the right side of the thorax, gross and microscopical changes, such as scattered haemorrhages under the pleura and in the lung tissue, oedema and emphysema of various degree were found in the right lung of both normergic and allergic animals. The changes of the left lung were in every instance similar but less extensive.

On the basis of the experiments reported it can be inferred that tuberculin injected intracutaneously over the lung exerts, besides its general effect, a local action (dermato-pulmonary reaction). A therapeutic inference can be drawn as to the possible influence on circumscribed specific pulmonary processes.

Tuberculin given intracutaneously causes in the lung a hyperergic reaction predominantly on the side of application. Whether or not this reaction has a specific character is not yet established.

SUMARIO

Después de una inyección intracutánea de tuberculina en el lado derecho del tórax, se observaron en el pulmón derecho de los animales tanto normérgicos como alérgicos, alteraciones macro- y microscópicas en forma de hemorragias esparcidas debajo de la pleura y en el tejido pulmonar, y edema y enfisema de mayor o menor intensidad. Las alteraciones del pulmón izquierdo fueron en todos los casos semejantes, pero menos extensas.

Tomando por base los experimentos comunicados, cabe deducir que la tuberculina inyectada intracutáneamente sobre el pulmón provoca, además de su efecto general, una acción local (reacción dermopulmonar). Puede hacerse una deducción terapéutica en cuanto al posible influjo sobre los procesos pulmonares específicos circunscritos.

La tuberculina administrada intracutáneamente provoca en el pulmón una reacción hiperérgica que predomina en el lado de la aplicación, pero no se ha establecido todavía si dicha reacción es o no específica.

REFERENCE

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LABORATORY AND CLINICAL NOTES

RAPID METHOD FOR THE CONCENTRATION OF TUBERCLE BACILLI[1]

JOSEPH OLIVER AND THEODORE R. REUSSER

One hesitates to report a new method for concentrating tubercle bacilli in suspected material when there are so many methods available. It is believed, however, that the method to be discussed has advantages over any of the procedures heretofore described. The technique for concentrating tubercle bacilli should be a method that is rapid and yet collecting the maximum number of tubercle bacilli per volume. The following method incorporates these features, giving several other advantages.

The digestant used in this method is Clorox, which is a solution manufactured by the Clorox Chemical Company for use as a bleacher, deodorizer and disinfectant. It contains as its active ingredient, 5.25 per cent sodium hypochlorite. Caustic soda, lime, acid and harsh substances have been removed and it can be used in perfect safety to the workers hands. Data accumulated by the manufacturer indicate that Clorox will contain over 5 per cent hypochlorite after six months storage or progress through distribution channels. Clorox can be purchased in any drug or grocery store for a few cents per quart bottle.

Clorox is similar to antiformin, which is an alkaline solution consisting essentially of equal parts of a 15 per cent solution of caustic soda and 20 per cent solution of sodium hypochlorite.

The method is so amazingly simple and rapid that even in the hands of ordinary laboratory workers it uniformly produces highly satisfactory results.

It has been found that most concentration methods in common use to-day require too much time in homogenizing and centrifuging the suspected material. Much bulky sediment by these methods defeat the purpose of concentration. The Clorox method eliminates both bulky sediments and long incubation for digestion. With this digestant the microscopical field shows a more even distribution than other methods. The fields are clearer with a minimum of background. Other organisms, pus, blood and mucus are completely digested, leaving a sediment consisting almost entirely of tubercle bacilli.

Method: Five to 10 cc. sputum are mixed in a flask or wide mouth bottle with approximately an equal amount of commercial Clorox and shaken two or three times over a two-minute period and kept at room temperature for ten minutes. Then the mixture is centrifuged at 3,000 revolutions for ten minutes in a 15 cc. conical tube. A creamy white sediment forms in the bottom of the test tube;

[1] From the Physicians' Clinical Laboratory, Tucson, Arizona.

the supernatant fluid is poured off and the tube is drained for two minutes. No neutralization is necessary. With an applicator a small drop of sediment is transferred to a slide. The slide dries at once and needs no fixing. Staining is done by the usual methods.

Table 1 shows the result of 300 sputa examined with Clorox and the sodium hydroxide method (1), 200 with the chemical flocculation method (2), 100 with the papain method (3) and 500 with direct smears of selected particles. In these studies 10 microscopical fields were examined and counted in each case. Two facts were brought to light which deserve special attention. First, not one positive was found by any method which was not also positive by Clorox, while on the other hand conclusive evidence is seen regarding the superiority of Clorox as a digestant. Second, in compiling the table there were cases observed in which the Clorox method actually demonstrated an increase in tubercle bacilli

TABLE 1

METHOD	NUMBER SPUTA	NUMBER POSITIVE	NUMBER NEGATIVE	AVERAGE NUMBER BACILLI PER FIELD*
Clorox	200	181	19	117
Chemical flocculation	200	167	33	39
Clorox	100	58	42	90
Papain	100	25	75	20
Clorox	300	271	29	85
Sodium hydroxide	300	223	77	23
Clorox	500	395	105	67
Direct smear	500	337	163	6

* On positive slides only.

of over 300 times that of direct smears of selected particles on the same specimen. In specimens repeatedly negative by direct smears, as high as 50 tubercle bacilli have been persistently found.

The 1,100 cases represented patients with various stages of tuberculosis from far advanced to moderately active and arrested. In each comparison the same amount of sputum was used and digestant in proportion to fill a 15 cc. centrifuge tube.

Clorox digestant has been found equally efficient in the concentration of tubercle bacilli in other body fluids. It has been tried with highly satisfactory results on urine, spinal fluids, chest aspirations and material from abscesses.

For determining the antiseptic power of Clorox, cultures were done on 30 positive cases after sputa were digested by this method. All cultures were negative at the end of forty-two days. This sterilizing feature is attractive to the laboratory worker from the standpoint of safety in handling the material.

SUMMARY

A method for the concentration of tubercle bacilli with Clorox in body fluids has been described, which has many advantages for the laboratory worker.

1. It is far more rapid than any previously described technique. Digestion is complete within two minutes.
2. It is economical.
3. There is no bulky sediment. The sediment consists mainly of tubercle bacilli.
4. The sediment needs no neutralization and fixing on the slide; it dries rapidly and can be stained by usual methods.
5. Tubercle bacilli are killed during digesting and centrifuging, thus making material safe for handling.

SUMARIO

Descríbese un método para la concentración de los bacilos tuberculosos en los humores orgánicos con Clorox, que presenta muchas ventajas para el laboratorista:

1. La técnica es mucho más rápida que ninguna descrita previamente, y complétase la digestión dentro de dos minutos.
2. Resulta económico.
3. No hay sedimento voluminoso, pues el sedimento consiste principalmente en bacilos tuberculosos.
4. El sedimento no necesita neutralización y fijación en el portaobjetos; se seca rápidamente y puede teñirse con las técnicas habituales.
5. Los bacilos tuberculosos quedan muertos durante la digestión y centrifugación, de modo que el material resulta inocuo para la manipulación.

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(3) Sullivan, N. P., and Sears, H. J.: A simple technique for concentrating tubercle bacilli in sputum, Ibid., 1939, *24*, 1093.

LIPOID PNEUMONIA[1]

Diagnosis by Aspiration Biopsy

JASON E. FARBER, ROBERT CARPENTER AND VICTOR PELLICANO

Lipoid or oil aspiration pneumonia is a recognized clinical entity. The symptoms, physical signs and roentgenographic findings are often those of a bronchopneumonia which may be protracted. The diagnosis is frequently made by exclusion of other conditions, for example, tuberculosis. A history of prolonged administration of oily substances by nose or mouth is suggestive. The use of aspiration biopsy in the diagnosis of difficult cases might seem warranted, providing routine diagnostic procedures are tried first. In the case being reported the diagnosis, although fairly evident, was verified in this manner.

L. G., a white housewife, aged forty-one, complained of chronic constipation of long standing and of chronic cough and expectoration, dyspnoea and pain in the chest since 1935. Since the onset of her illness the patient had been hospitalized in various institutions for spastic colitis, arthritis and chronic pneumonia. In December, 1934 the patient was given large amounts of mineral oil (30 cc. to 60 cc. t.i.d.) because of severe constipation. This treatment was continued intermittently for a period of one year. The patient experienced a "coughing and choking spell" each time she attempted to swallow the oil. The present illness began with pneumonia in February, 1935. In April, August and December of 1935 the patient suffered similar severe respiratory illnesses, each time diagnosed as pneumonia. Resolution of the lesion did not occur and in January, 1936 the patient was removed to a tuberculosis sanatorium where she remained for two years. Her sputum, however, was never positive for tubercle bacilli. When admitted to the Meyer Memorial Hospital (Service of Dr. G. G. Martin) in February, 1939 the patient supplied the foregoing anamnesis. In addition, it was learned that there had been a speech impairment since birth. At the age of twelve, the frenum of her tongue was incised because this was thought to be the cause of the speech defect. However, little improvement resulted. As a child, she also had difficulty in swallowing. This condition had become worse in recent years and lately she had suffered night sweats and chilly sensations.

On examination the patient appeared moderately well nourished but rather pale. Her speech was slow and she articulated poorly. There was dullness over the bases of the lungs. The breath sounds were bronchovesicular and medium coarse râles were heard in the same area. Neurological examination (Dr. F. Southworth) showed a residual right facial weakness and underdevelopment. There was asteognosis of the right hand. Deep reflexes were slightly more active on the left than on the right. There was a suggestive left Babinsky. The impression was gained that at birth there probably had been a haemorrhage into the right side of the medulla in the region of the *nucleus ambiguus*.

A roentgenogram of the chest taken on February 8, 1939 (figure 1) showed a hazy, homogeneous, diffuse bronchopneumonic infiltration in the right lower lung field below the eighth posterior rib. On the left side a rather similar hazy homogeneous density was

[1] From the Edward J. Meyer Memorial Hospital and the University of Buffalo Medical School, Buffalo, New York.

seen extending below the seventh posterior rib. On a direct lateral film the middle lobe appeared sharply outlined and densely infiltrated (figure 2).

The sputum was negative for tubercle bacilli and fungi. The Wassermann test and urine analysis were negative. There was a moderate iron-deficiency anaemia and a moderate leucocytosis. The erythrocyte sedimentation rate was 46 mm. per hour. The vital capacity was 1,150 cc., the normal standard being 3,000 cc.

The clinical course was uneventful and remained unchanged for months. The patient ran a low grade fever ranging between 97°F. and 99.2°F. All symptoms remained more or less the same. Râles were persistently heard in the bases of both lungs. Serial

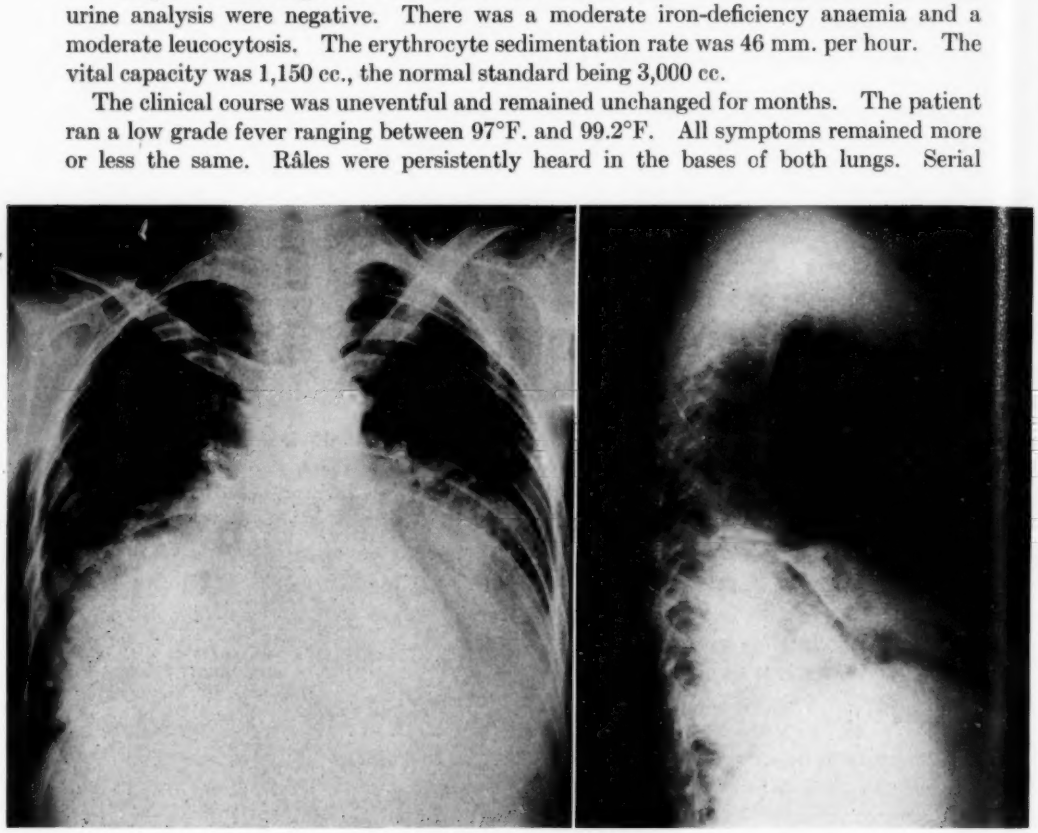

FIG. 1 FIG. 2

FIG. 1. Confluent bronchopneumonic infiltration due to aspiration of mineral oil.

FIG. 2. Lateral view shows the middle lobe of the right lung densely infiltrated by the pneumonic process.

roentgenograms showed essentially stationary pulmonary lesions. Bronchoscopy on two occasions was negative.

The clinical diagnosis was that of lipoid (mineral oil aspiration) pneumonia. It was finally decided to confirm the diagnosis by aspiration biopsy of the lung. A 16-gauge needle was inserted into the chest wall over the middle lobe of the right lung. Pleural symphysis was found and the needle was projected into the parenchyma. Approximately 3 cc. of a blood tinged oily fluid was obtained by aspiration. On standing this settled into a definite layer of oil over a layer of clotted blood. There was no untoward reaction following the procedure. Since then the patient has continued to run a fairly stable course except for a severe respiratory illness in January, 1941 when there was an increase in all symptoms, especially cough and expectoration.

SUMMARY

In the case reported routine diagnostic procedures suggested a diagnosis of lipoid pneumonia. On aspiration biopsy, oily fluid was removed from the lung. The cause of the aspiration of the oil in this patient cannot be definitely stated. However, the difficulty in swallowing might provide the necessary mechanism for the aspiration. On needle exploration of the chest, the pleural space was found to be obliterated. This point is cited because of the danger of both spontaneous pneumothorax and infection of the pleural space following needling of the thorax. In the presence of a free pleural space these dangers could be obviated by artificial obliteration of the space.

SUMARIO

En el caso comunicado, los habituales procedimientos diagnósticos indicaron la existencia de neumonía lipoidea. Una biopsia aspiratoria sólo extrajo un líquido oleoso del pulmón. No puede indicarse con seguridad la causa de la aspiración del aceite en este caso, pero la disfagia tal vez creara el mecanismo necesario. Al explorar con la aguja el tórax, se descubrió que el espacio pleural estaba obliterado. Cítase este punto debido al peligro que entrañan el neumotórax espontáneo así como la infección del espacio pleural después de introducirse una aguja en el tórax. En presencia de un espacio pleural libre, pueden evitarse estos peligros mediante la obliteración artificial del espacio.

A MEDIUM FOR BLOOD CULTURES IN RESPIRATORY INFECTIONS

CHARLES R. HUMBERT[1]

The search for a media for making blood cultures of organisms in respiratory disease has been conducted for a number of years. Many have been found useful for various types of organisms. The one accepted as most valuable in this laboratory is made from beef lung. When this work was begun some years ago fresh lung was used. Later the powdered lung has been donated by Armour Laboratories and Difco Company of Detroit for research purposes.

TABLE 1

RESPIRATORY INFECTION	NUMBER OF CASES	AGAR	NUTRIENT BOUILLON	BLOOD SERUM AGAR	DEXTROSE BRAIN BROTH	KRACKE'S BLOOD CULTURE MEDIUM	SERUM ACETIC AGAR	BLOOD AGAR	POWDERED LUNG MEDIUM
Lobar pneumonia	32	3	6	1	2	4	0	4	21
Bronchopneumonia	26	2	6	0	0	6	0	0	14
Lung abscess, primary	12	0	1	0	0	2	0	0	5
Lung abscess, secondary	4	0	0	0	0	0	0	0	2
Influenza	27	0	0	0	0	4	0	6	16

TABLE 2

Number of cases studied—101

CLASSIFICATION OF ORGANISMS	POSITIVE CULTURES	
	Lung medium	Other media
Staphylococcus	2	0
Pneumococcus	21	34
Streptococcus	5	3
Pfeiffer bacillus	16	10

The method used for making this media is as follows: one pound of fresh beef lung is cut in strips and ground in a meat chopper. It is soaked in cold water over night in the chill box. It is then cooked and filtered through cotton three times in order to remove particles of lung tissue. The filtrate is used just as beef infusion in other media.

The following formula has been found very serviceable:

Bouillon

Peptone	10 g.
Sodium chloride	5 g.
Lung infusion	1000 cc.

[1] Pathologist and Roentgenologist, Wheatley-Provident Hospital, and Visiting Physician at Kansas City General Hospital No. 2, Kansas City, Missouri.

Solid Medium

Agar agar	15 g.
Sodium chloride	5 g.
Lung infusion	1,000 cc.

If the powdered lung is used 120 g. in 1,000 cc. of water is soaked over night in the ice chest. It is then boiled and filtered. This filtrate is used as described above. The reaction is set at 7.8 pH.

Tables 1 and 2 show the results obtained with this and other media.

This medium has been useful in obtaining blood cultures in respiratory infections where others have failed. It is also used for many other organisms by adjusting the reaction suitable for their growth.

PRELIMINARY MEDICAL PROGRAM

National Tuberculosis Association—38th Annual Meeting
American Trudeau Society—37th Annual Meeting
Nat. Conference Tuberculosis Secretaries—18th Annual Meeting

PHILADELPHIA, PA.—MAY 6–9, 1942

All meetings will be held at the Bellevue-Stratford Hotel

Wednesday, May 6

9:30 A.M.

American Trudeau Society.....**Ball Room**

Presiding: HAROLD G. TRIMBLE, M.D., Oakland, Calif.

Business Meeting

Report of Secretary-Treasurer
Report of Membership Committee
Report of Committee on Nominations
Reports of Special Committees
Report of the Council

2:00 P.M.

Medical Section.....**Ball Room**

Panel Discussion on the Management of Patients with Occasional Positive Sputum After Apparently Adequate Therapy

Chairman: WILLIAM H. MONCRIEF, M.D., State Park, S. C.

Panel Discussion on the Treatment of Post-Operative Complications

Chairman: JOHN ALEXANDER, M.D., Ann Arbor, Mich.

Question Box Hour

Chairman: EMIL BOGEN, M.D., Olive View, Calif.

8:00 P.M.

General Meeting of the National Tuberculosis Association.....**Ball Room**

Report of Managing Director
President's Address
Award of Trudeau Medal
Report of Nominating Committee

Thursday, May 7

9:00 A.M.

Medical Section.....**Ball Room**

The Physiological Function of the Two Lungs Separately Under Varying Conditions

WALTER K. WHITEHEAD, M.D., Northville, Mich.

Discussion:

Observations on Contralateral Lung During Pneumothorax Treatment

FRANK L. JENNINGS, M.D. and P. M. MATTILL, M.D., Indianapolis, Ind.

Discussion:

The Clinical End Results of Pneumothorax

W. H. MORRISS, M.D., Wallingford, Conn.

Discussion:

Results of Eight Years' Experience of Artificial Pneumothorax Treatment in Ambulatory Patients
FREDERICK TICE, M.D., Chicago, Ill.
Discussion:
End Results of Extra-Pleural Pneumothorax
PAUL GEARY, M.D., Plainfield, N. J.
Discussion:

2:00 P.M.

Med. and Admin. Sections, Joint Session.....**Ball Room**
Historical Session
Chairman: RICHARD H. SHRYOCK, Ph.D., Philadelphia, Pa.
The Historical and Social Significance of the Tuberculosis Movement
RICHARD H. SHRYOCK, Ph.D.
The Problem of Tuberculosis Down to Koch's Discovery
GERALD B. WEBB, M.D., Colorado Springs, Colo.
The Periods of Organization from Koch to the NTA, 1882–1904
ROBERT G. PATERSON, Ph.D., Columbus, Ohio
Organization and Development of the National Tuberculosis Association
CHARLES J. HATFIELD, M.D., Philadelphia, Pa.
Modern Trends in the Control of Tuberculosis
ESMOND R. LONG, M.D., Philadelphia, Pa.
Medical Clinics:
Jefferson Hospital
Philadelphia General Hospital

Friday, May 8

9:30 A.M.

Medical Section.....**Ball Room**
Vitamin Nutrition in Tuberculosis
HORACE R. GETZ, M.D., and THEODORE A. KOERNER, M.D., Philadelphia, Pa.
Discussion:
The Prevention of Intestinal and Laryngeal Tuberculosis
MACK MCCONKEY, M.D., Ray Brook, N. Y.
Discussion:
Twin Studies on the Heredoconstitutional Variability of Tuberculosis
FRANZ J. KALLMANN, M.D., and DAVID REISNER, M.D., New York, N. Y.
Discussion:
Development of Tuberculosis in the Apparently Healthy Adult
ARTHUR B. ROBINS, M.D., New York, N. Y.
Discussion:
Technical and Economical Factors Associated with the Production of Miniature Chest Roentgenograms
S. REID WARREN, JR., Philadelphia, Pa.
Discussion:

2:00 P.M.

Medical Section.....**Ball Room**
The Roentgenographic–Pathologic Correlation of Tuberculous Calcifications in the Lung
ROBERT G. BLOCH, M.D., Chicago, Ill.
Discussion:

The Localization of Radio-Active Iron, Manganese and Cobalt in Experimental Tuberculosis

ALFRED GOLDMAN, M.D., and ALFRED MARSHAK, Ph.D., San Francisco, Calif.

The Development of Bronchoscopy

CHEVALIER L. JACKSON, M.D., Philadelphia, Pa.

Immunological Processes in Tuberculosis as Determined by Electrophoresis of the Blood

FLORENCE B. SEIBERT, Ph.D., Philadelphia, Pa.

Discussion:

The Effect of Promin on Experimental Tuberculosis in the Guinea Pig

W. H. FELDMAN, M.D., H. CORWIN HINSHAW, M.D., and F. C. MANN, M.D., Rochester, Minn.

Discussion:

Chemotherapy of Clinical Tuberculosis

H. CORWIN HINSHAW, M.D., Rochester, Minn.

Medical Clinics:

Temple University Hospital
University Hospital

8:30 P.M.

Medical Section.....**Ball Room**

Diagnostic and Therapeutic Clinical Conference

Chairman: HENRY C. SWEANY, M.D., Chicago, Ill.

Saturday, May 9

9:30 A.M.

Medical and Administrative Sections, Joint Session.....**Ball Room**

Medical Aspects of the Rehabilitation of the Tuberculous (A survey of the medical experience with approximately 1,000 tuberculous patients employed at Altro Work Shops, followed intensively over a twenty-five year period, 1915–1939)

LOUIS E. SILTZBACH, M.D., New York, N. Y.

Discussion:

Industry's Responsibility for the Worker's Health

G. H. GEHRMANN, M.D., Wilmington, Del.

Discussion:

Clinical Criteria for Determining Work Tolerance Following Pulmonary Tuberculosis

A. N. AITKEN, M.D., Lockport, N. Y.

Discussion:

The Need for Strengthened Social Services in Times of War—Based Upon Observations in Great Britain Under War Conditions

ERIC H. BIDDLE, Washington, D. C.

Tuberculosis and the War in England

J. B. MCDOUGALL, M.D., London, Paper to be read by G. J. WHERRETT, M.D., Ottawa, Can.

NOTICE

Conservation of Scholarly Journals

The American Library Association created this last year the Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the coöperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

NOTICE

The American Association for Thoracic Surgery announces that its annual meeting, which was scheduled to be held in St. Louis this year, has been called off due to the war.

THE CONTRALATERAL LUNG DURING PNEUMOTHORAX TREATMENT[1]

FRANK L. JENNINGS[2] AND P. M. MATTILL[3]

Rest has, for over one hundred years, been the mainstay in the treatment of pulmonary tuberculosis. It has been applied with increasing thoroughness throughout the years. It is the basis for artificial pneumothorax treatment. During the past twenty-five years, other surgical measures have been devised to bring about more rest to diseased lungs. It can be said that to-day the value of rest in the treatment of tuberculosis is much more thoroughly appreciated and applied than ever before.

The theory of rest in the treatment of tuberculosis led Forlanini and Murphy, and other early workers in artificial pneumothorax, to declare that pneumothorax should be confined to cases in which only one lung was diseased. While this is a good rule, even to-day, we do know that, if pneumothorax were given to those cases in which the disease was wholly confined to one lung, a majority of the patients would be denied a very beneficial therapeutic aid. Year by year, we have broadened the rules for the administration of artificial pneumothorax until to-day we do not hesitate to give it, even in the case of a well advanced lesion in the contralateral lung.

It is interesting to speculate on this theory of rest. With pneumothorax compressing one lung, we are safe in assuming that in the other lung there is exaggerated breathing; and with exaggerated breathing on the contralateral side, one would expect—if there was any tuberculosis in this contralateral lung—that it would be aggravated by compensatory breathing. It was this premise which prompted the study of lesions in the contralateral lung.

We have been giving artificial pneumothorax at Glen Lake Sanatorium for well over twenty years, and have recently reviewed all of the roentgen films on patients who had had artificial pneumothorax for a period of four to six months or more. The time of observation varied from less than one year—in a relatively few patients—to over fifteen years in 2 or 3 patients. The majority were observed from two to three years.

We classified the lesion in each lung before the patient had artificial pneumothorax, and then noted the changes which took place in these lungs—particularly the contralateral one—during the time the patients were under our care. For the purpose of this study, it seemed best to classify the lesion into three broad types, rather than follow the finer division which the roentgenologists had made. The classification which we used was as follows:

Fibroid: Lesions were usually small irregularly shaped or rounded, of moderate density and rather sharply outlined. They were usually found in the upper half of the lung.

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Fibrocavernous: Lesions were rather sharply demarcated, but larger and of greater density than the fibroid. Cavity formation was always present.
Exudative: Lesions were soft and fluffy in appearance, poorly defined and had a tendency to coalesce. Where coalescence had taken place, the lesion was that of tuberculous pneumonia.

In dividing the lesions, we have been aware of the fact that there could be different types of lesions in the same lung and also that the extent of the lesions had, usually, a very definite effect on end results.

In the hope that these variables might counterbalance one another, we elected to classify the questionable types of lesions by placing the cases in the group with the least favorable prognosis, that is, if a lung had a large amount of fibrosis and a cavity of small or moderate size, it was placed in the fibrocavernous group.

The entire group considered in this study is made up of those patients (578) who had unilateral collapse only and of a smaller number (67) who had collapse on both sides. All the patients in the unilateral group had had their pneumothorax for at least six months, while those with bilateral collapse had had unilateral pneumothorax for at least four months. (There were 15 who had the second side collapsed within four months and 5 within six months; thus making a total of 20 in whom the contralateral lung was collapsed within six months or less after establishing pneumothorax.) The larger number, 47, did not have the second side collapsed until more than six months had elapsed after the establishing of pneumothorax.

The average period for which the contralateral lung could be observed in the bilateral group, therefore, was somewhat less than for the unilateral group and for that reason they are presented separately.

The type of lesion that was found in each lung at the time pneumothorax was begun in the patients who had only unilateral collapse is shown in table 1. In all these, the tuberculosis was primarily unilateral even though the contralateral lung was considered entirely free from disease in but 135 patients.

Consideration in this study is given chiefly to the changes that occur in the contralateral lung after pneumothorax has been induced. However, the character of the lesion in the more diseased side is also of importance, since if uncontrolled there is eventually a spread to or increase in the disease in the contralateral lung.

The large majority (75 per cent) of all these patients had lesions which were classified as fibrocavernous. This approximates closely the number (77 per cent) of patients who enter the Sanatorium each year with cavitation (table 1).

It has not been our practice to collapse a massive frank tuberculous pneumonia. However, it was found expedient to treat 56 patients whose lesions were soft and which in many cases could be called small areas of pneumonia.

Fibroid lesions as a rule do not require collapse therapy and it is only after watching them for a period of time that such treatment may be indicated. During the period covered by this study, pneumothorax was used in only 50 patients with this type of lesion.

Twenty-seven patients were admitted with unilateral pneumothorax and it

was not possible to ascertain the type of lesion that was present before this therapy was started. Therefore, in this group, the study was confined to the changes observed in the contralateral lung while the patient was under our care.

The changes that occurred in the contralateral lung are recorded in table 2. It will be seen that our experience with exudative lesions and cavities was good. It has always been difficult for the physician to decide on pneumothorax treatment for the original lung when these types of lesions are present in the contra-

TABLE 1

Types of lesions when pneumothorax was started

ORIGINAL LUNG	TOTAL	CONTRALATERAL LUNG			
		Exudative	Fibro-cavernous	Fibroid	Negative
Exudative	56	2	2	35	17
Fibrocavernous	445	4	18	332	91
Fibroid	50		2	26	22
Collapsed*	27		2	20	5
Total	578	6	24	413	135

* Pneumothorax instituted prior to admission to sanatorium.

TABLE 2

Observations of contralateral lung

LESION IN CONTRALATERAL LUNG WHEN PNEUMOTHORAX WAS STARTED	TOTAL	REMAIN NEGATIVE	NO CHANGE	TUBERCULOSIS IMPROVED	UNSTABLE*	TUBERCULOSIS INCREASED†	TUBERCULOSIS DEVELOPED	NO RECORD
Exudative	6		1	5				
Fibrocavernous	24		3	10	3	7		1
Fibroid	413		201	122	23	64		3
Negative	135	126					8	1
No record								
Total	578	126	205	137	26	71 (12.2%)	8	5

* Lesions increased or decreased during period of observation, but in final analysis were neither better nor worse than found prior to pnx.

† Definite increase of lesion as observed by X-ray.

lateral lung. While the number of patients in these two groups is not large, it is our opinion that it is not so much the type of lesion in the contralateral lung, but its extent that should deter one in instituting collapse on the original side.

There were 71 patients in whom the tuberculosis increased and 8 in whom tuberculosis developed in the contralateral lung. It should be pointed out that in most instances these increases were small and in none was bilateral compression instituted. However, there were 4 in whom the pneumothorax was discontinued because of the increase in the disease in the contralateral lung. This occurred

in patients treated in the early days of this study; at a later date bilateral collapse would undoubtedly have been employed.

Tables 1 and 2 deal with observations of unilateral cases over a twenty-year period. Because the indications for inducing pneumothorax have changed materially during this interval, it seemed wise to divide the material into two groups—those who had pneumothorax induced during the first ten-year period and those who had their treatment begun during the second ten-year period.

TABLE 3

Bilateral pneumothorax—types of lesions prior to pneumothorax

ORIGINAL SIDE	TOTAL	CONTRALATERAL SIDE				
		Exudative	Fibrocavernous	Fibroid	Negative	No Record
Exudative	1	1				
Fibrocavernous	47	3	12	32		
Fibroid	7		1	6		
Collapse	10		3	7		
No record	2					2
Total	67	4 (5.97%)	16 (23.88%)	45 (67.16%)		2 (2.98%)

TABLE 4

Bilateral pneumothorax—observations of contralateral lung

LESION IN CONTRALATERAL LUNG AT TIME PNEUMOTHORAX INSTITUTED	TOTAL	CHANGES IN CONTRALATERAL LUNG						
		Remain negative	No change	Tuberculosis improved	Unstable	Tuberculosis increased	Tuberculosis developed	No record
Exudative	4					3		1
Fibrocavernous	16		1		3	12		
Fibroid	45		1		4	39		1
Negative								
No record	2					1	1	
Total	67		2 (2.98%)		7 (10.44%)	55 (82.08%)	1 (1.49%)	2 (2.98%)

During the first period pneumothorax was given much less frequently—usually after prolonged bed-rest had failed to give the desired results. During the last ten years the indications have been broadened until now most patients are considered suitable for pneumothorax, the exceptions being most minimal cases and those who appear hopelessly advanced. We were quite surprised to find that there was no material difference in the behavior of the contralateral lung in the two groups of cases; and we believe that the explanation lies in the fact that the majority of our patients (436) were treated in the last period. Had there been an equal number in each group, we believe that the earlier induction of pneu-

mothorax on the original side, as was the practice in the last ten years, would have brought about a more favorable effect in the contralateral lung.

The patients who comprise the smaller group (bilateral pneumothorax) are separated from those in the larger group because unilateral pneumothorax was maintained for a somewhat shorter period than the minimum time set for those patients who had compression on one side only and because bilateral collapse was instituted for changes that occurred in the contralateral lung. As our experience with bilateral collapse became more extensive it was found that this form of

TABLE 5

Types of lesions when pneumothorax was started—all cases

LESION IN ORIGINAL LUNG	TOTAL	LESION IN CONTRALATERAL LUNG				
		Exudative	Fibro-cavernous	Fibroid	Negative	No record
Exudative	57	3	2	35	17	
Fibrocavernous	492	7	30	364	91	
Fibroid	57		3	32	22	
Collapse	37		5	27	5	
No record	2					2
Total	645	10	40	458	135	2

TABLE 6

Observations of contralateral lung—all cases

LESIONS IN CONTRALATERAL LUNG	TOTAL	CHANGES IN LESION IN CONTRALATERAL LUNG						
		Remain neg.	No change	Tb. imp.	Unstable	Tb. incr.	Tb. devel.	No record
Exudative	10		1	5		3		1
Fibrocavernous	40		4	10	6	19		1
Fibroid	458		202	122	27	103		4
	508		*207 (40.7%)*	*137 (26.9%)*	*33 (6.5%)*	*125 (24.6%)*		
Negative	135	126					8	1
No record	2					1	1	
Total	645	126	207	137	33	126	9	7

treatment was well tolerated and it soon became apparent that one of the principal indications for bilateral pneumothorax was extension of the disease in the contralateral lung. This led to the acceptance of less rigid indications for instituting unilateral collapse for if bilateral collapse could be safely employed, then there need be less hesitation in starting a unilateral collapse. Thus, while for this group of patients only unilateral collapse was considered at the beginning of treatment, the possibility that bilateral compression could be done was always kept in mind. As a whole, this group had more extensive disease than did the larger one and it is our belief that this fact accounts in part at least for the larger

number in whom the disease increased in the contralateral lung (82 per cent as compared to 12 per cent). Approximately 30 per cent of the patients in the bilateral group had exudative and fibrocavernous disease in the contralateral lung as compared to 5 per cent of the unilateral group having similar types of lesions (tables 3 and 4).

In order to present our observations on all our patients without selection, we have combined tables 1 and 3 into table 5, which shows the type of lesions in the lung to be collapsed first (original lung) and also the type in the contralateral lung. Tables 2 and 4 have been combined in table 6 to show the changes which took place in the contralateral lung.

From these tables (5 and 6) we can obtain some rather broad working rules on patients who have bilateral tuberculosis, particularly if we omit those patients who had only unilateral disease and those whose records we do not have. There were 508 patients (table 6) who had tuberculosis in both lungs. In 207, or 40.7 per cent of them, there was no change in the disease in the contralateral lung. In 137, or 26.9 per cent, the disease improved. In 33, or 6.5 per cent, the disease was unstable but, in the end, neither better nor worse than at the time pneumothorax was started. There were 125, or 24.6 per cent, whose disease increased; but in 71 (unilateral group) the increase was not marked, except in 4, and bilateral compression was not done.

There were 135 patients whose contralateral lung was normal at the time pneumothorax was started. In 8, or 6.6 per cent of these, tuberculosis developed.

SUMMARY

Our experience has been that, given a patient with bilateral tuberculosis who was suitable for pneumothorax on one side, there was a 40 per cent chance that the lesion in the contralateral lung would not change, a 26 per cent chance that it would improve, a 6 per cent chance that it would be unstable, and lastly, a 24 per cent chance that the lesion would increase. This last 24 per cent may be divided into the 15 per cent of patients (71) who did not have collapse of the contralateral lung and the 9 per cent who did. Given a patient with a normal contralateral lung and the original lung suitable for pneumothorax, he will have a 6 per cent chance of developing tuberculosis in the good lung.

SUMMARIO

La experiencia de los autores demuestra que, presuponiendo un enfermo con tuberculosis bilateral apropiado para el neumotórax unilateral, hay 40 por ciento de probabilidades de que la lesión contralateral no se modificará, 26 por ciento de probabilidades de que mejorará, 6 por ciento de probabilidades de que no se estacionará, y por fin, 24 por ciento de probabilidades de que se agravará. Este último 24 por ciento puede dividirse entre el 15 por ciento (71 enfermos) en que no se aplastó el pulmón contralateral, y un 9 por ciento en que se aplastó. Dando por sentado un enfermo con un pulmón contralateral normal y el otro pulmón apropiado para el neumotórax, hay 6 por ciento de probabilidades de que se presente tuberculosis en el pulmón sano.

We wish to acknowledge our gratitude to Miss Anne McDonnell for the help she has given us with many of the details of this study.

CAUSES OF DEATH IN THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

ROBERT RITTERHOFF

Although there have been numerous reports, dealing principally with the late clinical results of thoracoplasty in the treatment of tuberculosis, little has been reported, other than lists of the causes of death, as to the pertinent necropsy findings in early fatal cases. The early operative mortality in this procedure has not significantly changed in the past five years, and appears to be somewhat uniform throughout the larger clinics. The relative and absolute reduction in the percentage of cases dying of wound infection from that reported by Hedblom and von Hazel in 1934 (1) suggests that patients previously regarded as poor risks are now being subjected to thoracoplasty. Should this concept be extended to include those in the older age groups, as has been recently advocated, one can logically expect to have an increase in early deaths, chiefly in that nebulous group of so-called "cardiorespiratory failures." Appropriately, then, more detailed reports of necropsy findings, particularly when correlated with extensive clinical and laboratory investigations, in early fatalities may demonstrate the mechanism or mechanisms involved, and thereby indirectly aid in the selection of suitable cases and in the further reduction of the operative mortality.

The group of thoracoplasties presented here includes 181 patients, subjected to 408 operations during the period from September, 1937 to July, 1941, under the supervision of Dr. B. N. Carter who, in 1936 (2), reported a preceding group of patients treated at his clinic. This present group consists of 91 males and 90 females whose mean age was 32.5 ± S.E.M. 0.6. Of all the fatalities, 11 male and 10 female, there were 16 early[3] deaths, of which 6 were males and 10 were females. The mean age of the early deaths was not significantly different from that of the entire thoracoplasty group. The fatality percentages were: total case fatality, 11.5; total operative fatality, 5; early case fatality, 9; and early operative fatality, 4. Analysis of the type of anaesthesia employed and the side of operation was noncontributory. However, there was a greater early fatality rate in cases undergoing first-stage and revision procedures in which the percentage fatalities were 18 and 20 per cent, respectively. This was considerably higher than in those subjected to the second and third stages, which had a percentage fatality of 4.7 and 6.4, respectively.

Analysis of 12 nonautopsied cases, of which 7 occurred within one month after operation, revealed that tuberculous bronchopneumonia, usually contralateral, was given as the cause of death in 4 of the early and in 4 of the late cases. This pneumonic process was associated with a homolateral empyema and broncho-

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[2] Presented at the Mississippi Valley Sanatorium Association meeting, October 3, 1941.

[3] Early—up to and including eight weeks postoperatively.

pleural fistula in one case in each group, one being present before operation and the other developing as a result of pleural laceration during a revision. However, in both cases the bronchopleural fistula probably developed postoperatively. The other 3 cases in the early group died of pneumococcic pneumonia, paradoxical respiration with mediastinal flutter, and postoperative shock, respectively. The remaining case of the late group died of cardiac failure, having findings compatible with so-called "chronic cor pulmonale." Two cases, one in each group, were obviously poor surgical risks as there was either roentgenographic or electrocardiographic evidence of cardiac disease. Finally, one case in the late group developed extensive bone and visceral tuberculosis after the third stage (table 1). This, essentially, has been the experience of others (1, 2, 3, 4, 5, 6), and without extensive postoperative laboratory investigation adds but little to previous knowledge. However, it does suggest that an underlying empyema, when placed under increased pressure as a result of thoracoplasty, may cause a bronchopleural fistula and its complications.

The necropsy findings on 9 early fatal cases, however, have been at some variance with the usual clinical causes of death and have further differed in that instead of "one cause of death," not infrequently several factors appear to be responsible. These cases can be roughly grouped into three clinical divisions: postoperative shock, inadequate respiratory reserve with or without paradoxical respiration and tuberculous pneumonia.

There were only 2 cases of tuberculous pneumonia in which the process at necropsy was thought to be extensive enough to be responsible for death. These cases are similar in that a small loculated tuberculous empyema with associated bronchopleural fistula was present in both.

Case W. 166, a twenty-nine year old white male, with bilateral mixed lesions, who died on the seventh postoperative day, following a left posterior revision with removal of segments of ribs 2, 3, 4 and 5 in one plate, under combined local and general anaesthesia. There was a large, thick-walled, partially compressed cavity filled with caseous material and extensive bronchogenic spread to the contralateral middle and lower lobes. The other case, *Z. 319*, a thirty-one year old white male, with bilateral mixed lesions, who died on the twenty-eighth postoperative day, following a right posterior second-stage thoracoplasty with removal of segments of the 5th, 6th and 7th ribs under combined local and general anaesthesia. He had a small thin-walled cavity which had broken into the pleural space and confluent foci of pneumonia, microscopically haematogenous, throughout both lungs, with dissemination to the abdominal viscera.

Thus, in addition to the mechanism of aspiration of infected cavity content to the contralateral lung, first demonstrated by McCordock and Ballon (7), it is also possible to aspirate empyema fluid, by way of a bronchopleural fistula, which has been placed under increased pressure as a result of thoracoplasty and paradoxical respiration. Also, tuberculous pneumonia may develop as a result of haematogenous dissemination, as illustrated by the second case. Other findings were those associated with terminal myocardial dilatation, namely, acute passive hyperaemia of the viscera, and anoxic encephalosis. This latter finding was most marked in the patient who lived twenty-eight days and was associated

TABLE 1

Nonautopsied thoracoplasty deaths (early—up to eight weeks)

CASE NUMBER	CLINICAL CAUSE OF DEATH	CONTRIBUTORY CAUSES	AGE, SEX, COLOR	STAGE OF THORACOPLASTY	DEATH OCCURRED	TYPE OF PULMONARY TUBERCULOSIS
Z. 538	Operative shock		38 WF	3rd posterior right	Day of operation	Unilateral productive
AA. 56	Paradoxical respiration, mediastinal flutter	Gastro-intestinal haemorrhage	28 WF	2nd posterior left	5th day postoperative	Bilateral mixed
X. 150	Contralateral pneumococcic pneumonia		19 WF	1st posterior right	7th day postoperative	Bilateral mixed
W. 428	Contralateral tuberculous pneumonia		29 WF	3rd posterior right	14th day postoperative	Unilateral exudative
Y. 328	Bilateral lower lobe tuberculous pneumonia	E.K.G.: heart block. Right ventricular predominance	29 BM	1st posterior right	1 month postoperative	Unilateral productive
X. 592	Contralateral tuberculous pneumonia	Wound infection, empyema, bronchopleural fistula	30 WF	Anterior revision of 2nd stage, left	1 month postoperative	Bilateral mixed
Y. 118	Contralateral tuberculous pneumonia		29 WF	3rd posterior right	1 month postoperative	Unilateral mixed
		(Late—after nine weeks)				
W. 386	Contralateral tuberculous pneumonia	Empyema. Bronchopleural fistula	34 WM	3rd posterior left	3 months postoperative	Bilateral mixed
X. 524	Contralateral tuberculous pneumonia	Suppurative cellulitis of neck	20 WM	3rd posterior right	7 months postoperative	Unilateral exudative
AB. 92	Tuberculous pericarditis or cor pulmonale		40 WM	2nd posterior right	19 months postoperative	Bilateral productive
X. 587	Bilateral lower lobe tuberculous pneumonia	Tuberculosis of spine and femur. Syphilis. E.K.G.: heart disease	30 BM	Posterior revision of 2nd stage, right	20 months postoperative	Unilateral exudative
U. 497	Bilateral lower lobe tuberculous pneumonia		38 WM	2nd posterior right	26 months postoperative	Bilateral productive

with focal subarachnoid cerebral haemorrhage. In these cases, then, the process was that of initial pneumonia with resultant toxaemia and respiratory insufficiency and subsequent cerebral anoxia and circulatory collapse.

Many authors (2, 8, 9, 10) believe that the anoxaemia due to insufficient respiratory reserve is frequently confused with heart failure and state that deaths due chiefly to myocardial failure are unusual. However, Moore, Humphreys and Cochrane state (11), "It was our feeling that not infrequently respiratory symptoms received an undue amount of attention because they are so obvious and so easy to interpret, whereas the true significance of circulatory change, which is more obscure and harder to explain, is sometimes unappreciated or completely overlooked."

The second group of patients (table 2), whose deaths were clinically considered as principally resulting from respiratory failure, all developed at various times postoperatively slight to moderate dyspnoea, which at the onset was not associated with cyanosis. Later, alternating periods of hyperpnoea and bradypnoea occurred which, when accompanied by paradoxical respiration, usually were associated with cyanosis. Oxygen therapy and measures taken to control paradoxical thoracic movement temporarily relieved the cyanosis; however, the altered respiratory rhythm would persist. Up to this time no striking cardiovascular changes would be apparent except for an increased pulse rate. Terminally, persistent cyanosis, falling blood pressure, Cheyne-Stokes respiration, stupor and acapnoea developed. None of these patients had any previous history of hypertension, nor microscopically was there any evidence of systemic arteriolar or diffuse renal disease which might have produced left ventricular strain. Grossly, the hearts were dilated and all had thickened right ventricular columnae carneae and papillary muscles. To determine the presence of minor degrees of cardiac hypertrophy, Zeek's (12) body-length:heart-weight ratio was employed. Approximately, this is normally 1.6 for females and 1.8 for males ± 0.2. On this basis the two obvious cases of cardiac hypertrophy were well above the normal variation. One case, X. 655, had equivocal hypertrophy, and the other two, Z. 309 and X. 287, were within normal range. Apparently, slight or moderate right ventricular hypertrophy produces relatively little change in the total heart weight, for in the reported cases of right ventricular hypertrophy, either from long standing pulmonary tuberculosis (13, 14) or embolic occulsion of the pulmonary arterioles (15, 16), the heart weight has been as low as 325 g. This, also, has been noted in experimental work on dogs in which the small arterioles were occluded (17). Thompson and White (18) estimated that an increased pulmonary blood pressure for about two months is necessary to produce appreciable hypertrophy of the right ventricle. Thus, case Y. 282, presenting definite right heart hypertrophy, may well have developed this following the second stage, which was done two weeks after the first and nine and one-half months prior to the third. That myocardial failure was present in this group was evident from the findings of various degrees of chronic passive hyperaemia of the viscera, depending upon the length of life postoperatively. The contralateral lung and that not collapsed as a result of thoracoplasty gen-

TABLE 2

Summary of the significant findings in the second group of necropsied cases

CASE NUMBER	CLINICAL CAUSE OF DEATH	AGE, SEX, COLOR	STAGE OF THORACOPLASTY	DEATH OCCURRED	TYPE OF PULMONARY TUBERCULOSIS	HEART WEIGHT IN GRAMS, BODY LENGTH RATIO	NEPHROSIS OF "ALKALOSIS"	FAT EMBOLI
Z. 309	Inadequate pulmonary reserve. Cardiac failure	49 WF	1st posterior right	3rd day post-operative	Unilateral productive	290 1.82	0	Minimal pulmonary
X. 92	Probable tuberculous pneumonia. Gastro-enteric haemorrhage	51 WM	1st posterior right	6th day post-operative	Unilateral mixed	600 3.39	0	No stains made
Y. 282	Probable tuberculous pneumonia. Paradoxical respiration	32 WF	3rd posterior right	16th day post-operative	Bilateral productive	400 2.46	Marked	Massive pulmonary and renal
X. 287	Inadequate pulmonary reserve	37 WM	2nd posterior left	1 month post-operative	Bilateral mixed	340 2.0	Marked, with focal calcification	Minimal pulmonary
X. 655	Inadequate pulmonary reserve, with early tuberculous bronchopneumonia	28 BF	Revision, left posterior	1 month post-operative	Bilateral mixed	315 1.96	Marked	0

erally presented marked chronic pulmonary emphysema, focal areas of fibrosis and fibrocaseous and caseous tuberculosis, marked oedema and acute passive hyperaemia, with focal extravasations of erythrocytes.

There is some uniformity of opinion regarding the pathological physiology of the cardiovascular and pulmonary systems incident to thoracoplasty. With the demand for increased function of the contralateral lung, its capillaries are dilated and engorged, resulting in decreased pulmonary distensibility and, hence, increased strain upon the right heart (19). In addition, Adams (20) has shown that there is a decreased percentage volume flow through the atelectatic lung, which would necessitate a larger percentage volume flow through the contralateral lung. As a result of engorgement of the pulmonary vascular tree and distention of the lung there is a decrease in the vital capacity and hyperpnoea ensues by way of the Hering-Breuer reflex. Paradoxical respirations will cause further embarrassment. With hyperpnoea carbon dioxide will be washed out of the blood stream, as is evidenced by high carbon dioxide concentrations of the alveolar air found in patients after thoracoplasty (3). Lowered carbon dioxide content of arterial blood will decrease oxyhaemoglobin dissociation and eventuate in tissue anoxia. The experimental work of Fineberg and Wiggers (21) has shown that the right ventricle is able to compensate for compression of the pulmonary artery up to 48 per cent without any change in cardiac output, although increased initial right intraventricular pressure is definitely demonstrable at 40 per cent compression. Beginning at 56 per cent compression there is a decreased left ventricular output and at 60 per cent, total failure of compensation. They also have shown that, should compression be maintained at the point of adequate dynamic compensation, 52 per cent, for a considerable period of time, progressive failure is likely to supervene. As soon as decreased cardiac output ensues, coronary blood flow is decreased to the already strained right ventricle. This investigation by Fineberg and Wiggers (21) emphasizes that the right ventricle has only a limited response to sudden increases in pulmonary resistance which, when accompanied by some degree of anoxaemia, will result in hypodynamia of the right ventricular muscle. Given, then, a patient with a lowered cardiorespiratory reserve as a result of long standing pulmonary tuberculosis or previous thoracoplasty, not clinically severe enough to produce signs and symptoms of right heart strain, if the burden of an already taxed lesser circulation is suddenly increased, the findings of right heart dilatation with various degrees of hypertrophy in association with visceral evidences of heart failure cannot be disregarded in the explanation of death.

Decker (6) has commented upon the number of patients having "nephritis" after thoracoplasty; however, the diagnosis of the type and what subsequent studies revealed were not given. Interesting departures from normal were present in the kidneys of one of the cases in the first and of 3 cases in the second group. All of these patients lived sixteen days or longer after operation; however, urine studies, other than in one case, were made only on the day following operation, despite slight albuminuria, acid urine and casts which were invariably present. Grossly, the kidneys were swollen and of increased weight, varying

from 300 to 370 g. Microscopically, the alterations were most marked in the convoluted tubules and to a lesser extent in the loops of Henle. Occasionally, changes were present in the collecting tubules. There was moderate generalized toxic nephrosis; however, in the areas mentioned there was marked degeneration with necrosis, occasional epithelial sloughs lying in the lumina of the tubules, with low cuboidal epithelial regeneration, and small globular masses, either acidophilic or basophilic, between the basement membrane and partially sloughed epithelium. Necrotic epithelial sloughs appeared as deeply basophilic granular casts. The majority of casts were acidophilic, hyaline and partially fractured. In the earliest stage of formation they consisted of small fused globules, usually acidophilic, of varying sizes. The larger casts, and apparently older, were usually somewhat basophilic and contained small faint globules; these casts on cross section appeared as concentrically laminated round bodies traversed by fracture lines. Similar renal changes have been reported in cases of alkalosis due to pyloric or high intestinal obstruction (22). Also (23), it has been shown that haemoglobinuria can be produced in dogs by hyperventilation. Von Kossa's calcium stain and the Prussian blue stain were employed to identify the character of the granular basophilic casts; these stains were positive in only one case, X. 287. Negative specific stains for haemosiderin and equivocal stains for calcium in the other cases do not preclude the possibility of this material being either haemofuchsin or calcospherites, or both. Clinically, a state of alkalosis was not suspected and blood chemical analyses, possibly confirmatory, were not done. A respiratory alkalosis, as the renal lesions indicate, can in itself initiate or contribute to a series of events not unlike cardiorespiratory failure; namely, pulmonary oedema, stupor, alternating periods of dyspnoea, fast pulse and weak heart action (24).

Fat embolism, which occurred in 3 cases, 2 minimal pulmonary and one massive in which there was renal and pulmonary involvement, was another microscopical finding in the second group of cases. This condition, often regarded as a clinical curiosity and frequently forgotten as a possible factor in deaths in which the cause is obscure, should prove to be a more frequent necropsy finding in patients who die shortly after thoracoplasty. For, one of the chief factors necessary in the production of fat emboli, trauma to subcutaneous, intermuscular and osseous medullary fat deposits, with subsequent liquefaction of fat, is produced by this type of surgical procedure. Further, the mechanism by which fluid fat is forced into the venous circulation is readily explained by the "sucking action" on venous thoracic osseous blood flow by the act of inspiration. Lehman and Moore (25), in view of the fact that fracture of bone is not necessary to produce fat emboli, believe that there is a severe systemic derangement of fat metabolism produced by the liberation of "shock material," which has been termed lipoproteinase (26). Usually, the symptoms are those of initial shock and, following a variable latent period, dyspnoea, cyanosis, sense of thoracic constriction, and pulmonary oedema appear. Signs of systemic dissemination may develop a few days after the trauma, such as delirium, hyperpyrexia, coma, fat globules in the urine and in the retinal vessels. On the basis of Scuderi's

(27) and Lehman and Moore's (25) experimental work, between 50 and 120 cc. of fluid fat would be necessary to produce a lethal outcome in man. Vance (28) in his study of the significance of fat embolism concluded that fat embolism associated with shock is more serious than shock alone, that moderate or marked pulmonary embolism may account for death and that massive pulmonary involvement with systemic dissemination is a significant cause of death. In several of the reported series, pulmonary embolism and cerebral haemorrhage have been given as the "clinical" (information as to necropsy not available) cause of death. In 2 cases presented here, with minimal fat emboli there were no unusual clinical findings which may have pointed to this phenomenon. The case of massive pulmonary and renal fat embolism developed coma and central type of respiration; fat globules appeared in the urine the day before death. Pathologically this case presented moderate right ventricular hypertrophy.

These findings of evidences of heart failure with occasional right ventricular hypertrophy, either alone or in association with fat embolism and possible alkalosis, all of which can produce conspicuous respiratory signs, clearly demonstrate the multiplicity of factors operative in the cases whose death clinically appeared to be from respiratory failure. Examination of the central nervous system was not permitted in a sufficient number of these cases to evaluate the probable cytological alterations accompanying anoxia.

The remaining two necropsied cases, both with unilateral productive lesions, died of postoperative shock. *Case AA. 433*, a twenty-four year old Negress, died on the day of operation, following a right posterior revision with removal of rib segments 1 to 8 inclusive under combined local and general anaesthesia. *Case U. 566*, a forty-four year old white male, died on the first postoperative day following a left posterior second-stage thoracoplasty with removal of rib segments 4 to 7 inclusive, under local anaesthesia. The only significant gross and microscopical necropsy finding, other than acute passive hyperaemia of the viscera, was that of moderate pulmonary fat embolism in case U. 566.

That there is considerable tissue trauma incident to a thoracoplasty is evidenced by these cases of fat embolism and by one case of postoperative moderate gastro-enteric haemorrhage in which was found acute focal ulcerative eosophagitis and duodenitis, which have been shown to be associated with surgical shock (29).

SUMMARY

There were 21 deaths in a series of 181 patients subjected to 408 thoracoplasties. Necropsies were performed on 9 of the 16 patients who died within one month following operation. Analysis of this group of necropsies demonstrates that a variety of factors may be operative in early deaths following thoracoplasty. This is in keeping with the principle that injury to one of a group of systems, anatomically and physiologically related, is reflected by departures from normal in the other related systems. This variety of factors is particularly conspicuous in the second group of cases, in that right cardiac hypertrophy, cardiac dilatation, changes suggestive of alkalosis, and fat embolism were prom-

inent pathological findings. However, these were not clinically evaluated, being interpreted as respiratory failure with or without tuberculous bronchopneumonia.

The presence of fat embolism and focal ulcerative eosophagitis and duodenitis emphasizes that even with present surgical technique, thoracoplasty is still attended by considerable trauma. This is particularly true in revision procedures which are usually more extensive than the primary operations.

Altered thoracic aerodynamics, either induced by paradoxical respiration or increased pulmonary circulation pressure, may result in alkalosis and tissue anoxaemia.

Contralateral tuberculous bronchopneumonia may result from aspiration of an empyema by way of a bronchopleural fistula or from blood stream distribution of infectious material. This complication, clinically thought to be a frequent cause of death, was pathologically significant in only 2 cases.

More extensive clinical and laboratory postoperative investigations, particularly when correlated with complete necropsy findings, will establish the development of events and their relative significance in thoracoplasty fatalities.

SUMARIO

Entre 181 tuberculosos que fueron objeto de 408 toracoplastias sobrevinieron 21 muertes. En 9 de los 16 que murieron dentro de un mes después de la operación, se realizaron autopsias, y el análisis de este grupo demuestra que pueden intervenir varios factores en las muertes tempranas consecutivas a la toracoplastia. Esto armoniza con el principio de que, en un grupo de sistemas relacionados anatómica y fisiológicamente, la lesión de uno de ellos se refleja en desviaciones de lo normal en los otros sistemas relacionados. La variedad de estos factores se hace notar en particular en el segundo grupo de casos, en el que la hipertrofia del corazón derecho, la dilatación cardíaca, las alteraciones indicativas de alcalosis y de embolia grasa, constituyeron sobresalientes hallazgos patológicos. Sin embargo, no se justipreciaron clínicamente, interpretándose como insuficiencia respiratoria con o sin bronconeumonía tuberculosa.

La presencia de embolia grasa y de esofagitis y duodenitis ulceradas focales pone de manifiesto que, aun con las actuales técnicas quirúrgicas, la toracoplastia va acompañada de considerable traumatismo, sobre todo en los procedimientos revisores que suelen ser más extensos que las intervenciones primarias.

La alteración de la aerodinamia torácica, provocada bien por la respiración paradójica o la aumentada presión de la circulación pulmonar, puede dar por resultado alcalosis y anoxemia histológica.

También puede sobrevenir bronconeumonía tuberculosa contralateral debido a la aspiración de un empiema a través de una fístula broncopleural o difusión circulatoria de substancias infecciosas. Esta complicación, que clínicamente pasa por ser causa frecuente de mortalidad, sólo revistió importancia patológica en 2 casos.

Más extensas investigaciones postoperatorias que comprendan tanto datos clínicos como de laboratorio, en particular si se correlacionan con completos

hallazgos autópsicos, establecerán la evolución de los acontecimientos y su relativa importancia en la mortalidad toracoplástica.

The two significant cases of fat embolism in this report, Y. 282 and U. 566, have been recently reported by Carter *et al.* (30). Reinvestigation and more extensive study of these cases disclosed that kidney changes suggestive of alkalosis and cor pulmonale were additional findings in case Y. 282.

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ENDOBRONCHIAL TUBERCULOSIS[1]

Its Rôle in Causing Rapid Reëxpansion or Atelectasis of the Lung following Closed Pneumonolysis

OTTO C. BRANTIGAN, REUBEN HOFFMAN AND DONALD F. PROCTOR

The increasing use of bronchoscopy in tuberculous patients has revealed a significant percentage of pulmonary lesions to be complicated by endobronchial lesions (1, 2, 3). Along with this knowledge there has been a growing appreciation of the rôle that these lesions play in influencing the course of the parenchymal disease. There are various pathological conditions that endobronchial lesions institute and the subsequent clinico-pathological course is dependent upon the degree and permanence of the bronchial occlusion.

The purpose of this communication is to call attention to the part that endobronchial lesions play in causing rapid reëxpansion of the lung or atelectasis following closed intrapleural pneumonolysis. In the presence of an endobronchial lesion a closed pneumonolysis may be followed by either the creation of a check-valve mechanism resulting in rapid reëxpansion of the lung or by complete occlusion resulting in atelectasis. The increased collapse of the lung and the kinking of the bronchus which follow closed pneumonolysis, together with the type of lesion and its location, and the character of the secretions are the factors that bring about either reëxpansion or atelectasis.

Recently, we encountered 4 patients in whom closed pneumonolysis was followed by rapid reëxpansion and loss of the pneumothorax space. Fluoroscopic examinations were performed three hours after the completion of the pneumonolysis, at which time almost complete reëxpansion was observed. Marked subcutaneous emphysema was evident. Pneumothorax refills were immediately administered and repeated within four hours. The following morning complete reëxpansion had occurred in one case, evidenced by fluoroscopy and inability to obtain a manometric reading indicative of a free pleural space; in the other 3 cases, the upper and middle lobes had reëxpanded, but there was a partial collapse of the lower lobe. Along with the frequent refills there was an increasing amount of subcutaneous emphysema.

The accepted explanation for the loss of the pneumothorax space following a closed pneumonolysis is excessive leakage of air through the wounds made by the thoracoscopic instruments. Unless a special technique is employed (4), the openings in the pleura cannot be made air-tight and remain an avenue for the escape of air. We do not consider excessive leakage of air *per se* as the cause of the reëxpansion of the lung. If the mere escape of air through the puncture wounds is the cause of the loss of the pneumothorax space, then it should occur in varying degrees in all patients. Actually, the great majority of patients in whom closed pneumonolysis is performed show very little evidence of reëxpansion (usually none) and very little subcutaneous emphysema.

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The presence of an endobronchial lesion in the main-stem bronchus, at the orifice of the branch bronchus, or within the lumen of the branch bronchus explains the rapid loss of air in the following manner. After severance of the adhesions there is an increase in the amount of pulmonary collapse and a certain degree of kinking of the bronchus. These two factors together with the endobronchial lesion and the retained secretions precipitate obstruction of the bronchus. The obstruction, however, is of the check-valve type, allowing ingress of air into the affected lung (or lobe), but preventing its escape. Every inspiration, therefore, is followed by the trapping of the air in the lung with its ultimate complete inflation.

It follows that the subcutaneous emphysema is the *result* of the reëxpanded lung and *not the cause*. It also explains why frequent refills fail to prevent the reëxpansion of the lung, inasmuch as the injected air is driven out by the expanding lung into the subcutaneous tissue through the openings in the parietal pleura. Where there is reëxpansion of the entire lung, it can be expected that the amount of subcutaneous emphysema will increase as refills are given more frequently. Where there is reëxpansion of a lobe(s), the residual pneumothorax space accommodates a portion of the injected air and the subcutaneous emphysema may not be as marked.

Subsequent bronchoscopy in all four cases revealed endobronchial lesions at the orifices of the branch bronchi which had caused partial obstruction. The following case history illustrates the phenomenon of rapid reëxpansion following a closed pneumonolysis.

E. P., colored female, twenty-eight, was admitted to the sanatorium on January 31, 1941 with a history of an illness that began two months prior to admission. An X-ray film revealed a 3 cm. cavity under the left clavicle with surrounding infiltration. Sputum was positive for tubercle bacilli. Pneumothorax was induced on February 8, 1941, resulting in an incomplete pneumothorax collapse due to the presence of a broad, triangular adhesion. On May 8, 1941 a thoracoscopic examination was performed; several ramifying folds of adhesions were seen and freed from their attachments to the chest wall. Three hours after completion of the closed pneumonolysis there was marked subcutaneous emphysema and fluoroscopic evidence of almost complete reëxpansion of the lung. A refill was immediately given, followed by another one in four hours. The following morning fluoroscopy indicated complete reëxpansion, a free pleural space could not be found and there was marked subcutaneous emphysema.

Bronchoscopy one week later revealed the mucous membrane of the left upper lobe bronchus to be thick and reddened and the orifice of the left upper lobe bronchus to be the site of thickened, reddened granulation tissue causing marked narrowing of the bronchial lumen. A large amount of purulent material was seen oozing from the mouth of the bronchus (figures a and b).

In contrast to the check-valve type of obstruction which causes rapid reëxpansion of the lung, the closed pneumonolysis may be followed by complete obstruction resulting in atelectasis. Again, the atelectasis may involve the whole lung or it may be lobar, depending upon the location of the lesion(s). Complete atelectasis following closed pneumonolysis was observed in 2 cases. Subsequent

bronchoscopy in both cases revealed extensive endobronchial lesions at the orifices of the bronchi with almost complete obstruction. The following history illustrates this type of case.

M.I.S., colored female, twenty-four, was admitted to the sanatorium April 4, 1941 with a history that her illness began the previous month with cough and night sweats. Admission X-ray film showed caseous-pneumonic disease in the upper half of the left lung containing several small cavities. Sputum was positive for tubercle bacilli. Pneumothorax was induced on April 21, 1941. Adhesions prevented a satisfactory collapse and on May 13, 1941 a thoracoscopic examination was performed, at which time an extensively ramifying fold adhesion was seen. This fold adhesion was completely removed from its attachment to the chest wall. Three hours after completion of the pneumonolysis, fluoroscopy showed the lung to be completely collapsed. There was no subcutaneous emphysema.

Bronchoscopy was performed two weeks later at which time the left upper lobe orifice was seen to be red and congested. Six centimetres below this point, in the left lower lobe bronchus, the mucous membrane was irregular, causing almost complete occlusion of the bronchial lumen.

Two oxygen lavages of the pleural cavity were subsequently performed. Each lavage was followed by a 25 per cent reëxpansion of the lung; however, in one week (after each lavage), the lung again completely collapsed.

Granting the validity of the explanation of the rapid reëxpansion as described, other commonly encountered conditions associated with artificial pneumothorax may be explained on the same basis. May not the development of an endobronchial lesion, or the progression of a previously existing one, account for spontaneous reëxpansion of the lung, maintained by artificial pneumothorax, in the known absence of adhesions? We have encountered one case of progressive reëxpansion where bronchoscopy revealed a definite ulceration, with partial occlusion, in the lower lobe bronchus on the pneumothorax side.

Although we have not had the opportunity to bronchoscope any patient in whom rather sudden spontaneous reëxpansion has occurred (in the absence of adhesions), we feel certain that bronchoscopy, when performed, will show an endobronchial, occlusive lesion.

May not the inability to accomplish a collapse of the lung with pneumothorax, beyond a certain point, in the absence of adhesions, be explained on the same basis? Here a moderate degree of collapse may precipitate the check-valve obstruction and by the consequent increased intrapulmonic pressure prevent further collapse. The only evidence that can be offered is one case in which a partial pneumothorax could be maintained only by frequent refills with positive pressures. No adhesions could be seen and there was no evidence that pointed to their existence. Bronchoscopy was performed and a lesion was found in the lower lobe bronchus on the pneumothorax side, along with the presence of tenacious secretions which were aspirated. Following bronchoscopy the patient was able to take larger refills with negative pressures and there was an increase in the amount of collapse.

It is difficult and sometimes impossible to reëxpand a lung that has been col-

lapsed by pneumothorax. Farber (5) reported 2 cases where failure to reëxpand was based on a stenotic endobronchial lesion where marked secondary changes (fibrosis and abscess formation) existed. However, some lungs are difficult or impossible to reëxpand even where the collapse has not been of sufficient duration to expect any marked secondary changes. In these cases, failure to reëxpand the lung may be due to the fact that the complete bronchial occlusion prevents any air from reaching the lung. Even where highly negative intrapleural pressures can be obtained, as in oxygen lavage of the pleural cavity, we have encountered lungs that could not be reëxpanded. In these cases, bronchopleural fistulae (the other condition that would prevent reëxpansion) have been ruled out.

The preoperative treatment would require routine bronchoscopy in any individual on whom a closed pneumonolysis is to be performed. If a lesion is seen, it should be treated by the topical application of silver nitrate, or some shrinking agent, in an attempt to cause sufficient reduction in the size of the lesion to obviate the potential obstruction. We have treated one case in this manner. The pneumonolysis was performed after two applications of silver nitrate to a lesion at the orifice of the upper lobe bronchus that had caused marked obstruction. Subsequently, the pneumonolysis was successfully performed without the occurrence of either rapid reëxpansion or atelectasis.

This patient, six weeks after pneumonolysis, showed definite evidence of reëxpansion, both radiographically and manometrically. Serial X-ray films have shown a progressive reëxpansion. Up until this reëxpansion began, patient was

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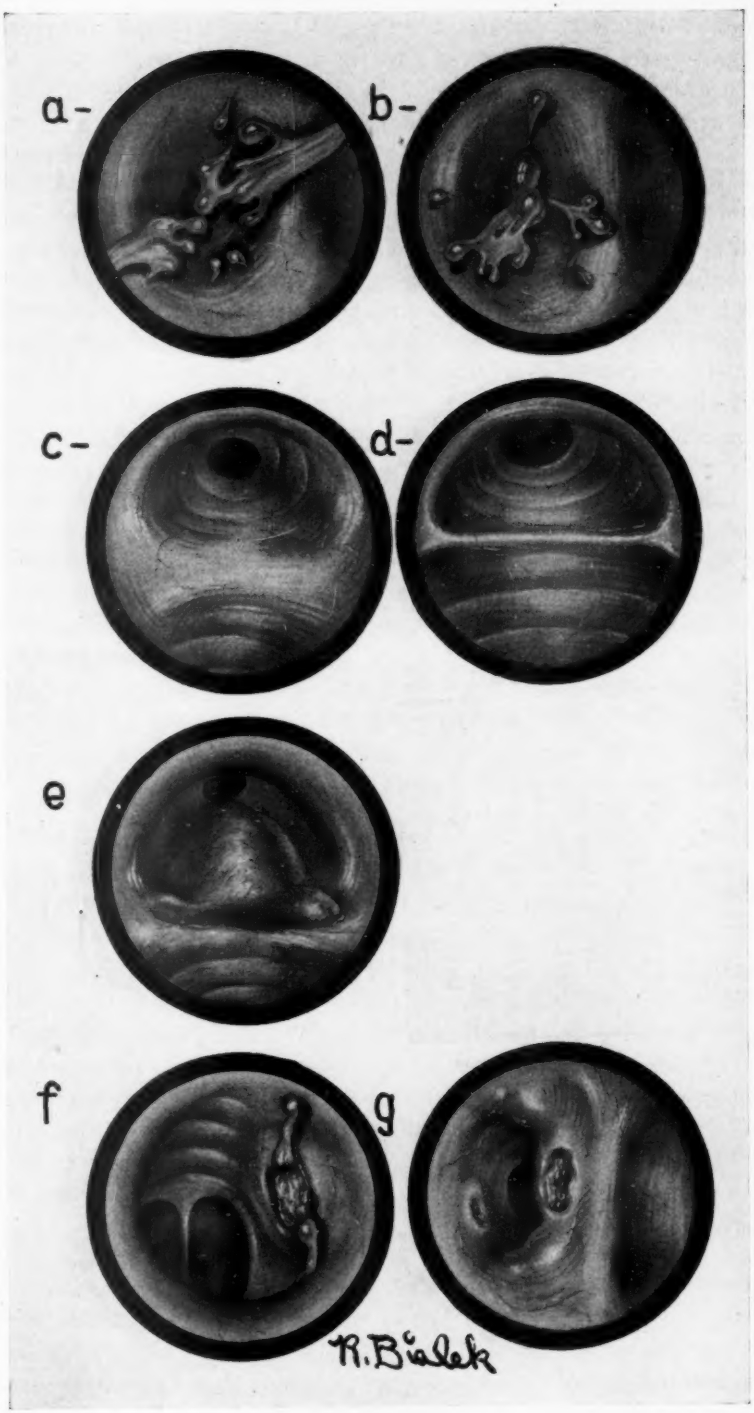
FIGS. a and b. Patient in whom closed intrapleural pneumonolysis was followed by rapid reëxpansion and loss of pneumothorax space. Figure a shows the bronchoscopic view in inspiration; figure b, the same view in expiration. It will be noted that in figure a the lumen of the left upper lobe orifice is markedly stenotic and covered with purulent secretions which were observed coming from the orifice. In expiration, figure b, the lumen is completely occluded by the secretions that have shifted over and plugged the orifice. It can be seen that air enters the partially occluded lumen during inspiration, but is prevented from escaping during expiration. Each inspiration, therefore, results in raising the intrapulmonic pressure and causing the ultimate complete inflation of the collapsed lung.

FIG. c. Patient in whom closed pneumonolysis was followed by rapid reëxpansion and loss of pneumothorax space. Figure c shows thickening of the orifice of the right middle lobe bronchus and about 50 per cent reduction in the size of the lumen. Although secretions were not seen at the mouth of the lumen, there is no valid objection in postulating their presence at a point distal to the luminal opening. The narrowed lumen, in the great majority of cases, sets the stage for the obstruction, the tenacious secretions serving as the final occluding mechanism.

FIG. d. This figure is the bronchoscopic view of a normal right middle lobe orifice offered as contrast.

FIG. e. Case of rapid reëxpansion following closed pneumonolysis. Figure e shows the bronchoscopic view of a right middle lobe bronchus in which marked narrowing of the lumen is evident along with a rather large, projecting, granulomatous mass encroaching upon the opening.

FIGS. f and g. Case of progressive reëxpansion in a patient receiving artificial pneumothorax without any evidence of adhesions or obliterative pleuritis. In figure f lesions are seen distal to the carina and on the medial wall of the main left bronchus; also a lesion superior to the left upper lobe bronchus, on the lateral wall. Reduction in the size of the lumen of the left upper lobe bronchus is seen in figure g.



FIGS. a–g

able to take 300 to 400 cc. of air with a negative terminal pressure; now 75 cc. of air produces a terminal pressure of plus 10.

Two bronchoscopies have shown a decided worsening of the lesion with the bronchus almost completely occluded and acutely inflamed. Two topical applications of 30 per cent silver nitrate have had no effect upon relieving the obstruction.

This incident offers further evidence that the explanation for the reëxpansion of an artificial pneumothorax (in the absence of adhesions) is correct.

Since only a small percentage of cases of closed pneumonolysis is followed by rapid reëxpansion or atelectasis and since all endobronchial lesions are not necessarily followed by one or the other of these complications, routine bronchoscopy before operation may be deemed unnecessary. Treatment, however, should be promptly instituted in any case where rapid reëxpansion has occurred. Enough shrinkage of the lesion may be effected to reopen the bronchial lumen and so allow the reinduction of the pneumothorax. We do not believe that the lung becomes adherent within two or three days, since it is unlikely that any degree of pleural symphysis occurs within that period of time, particularly where the two pleurae are uninvolved. Further belief that the pneumothorax can be reinduced is based on reports by Shamaskin and Rogoff (6), Hayes and Brown (7), and Voorsanger (8). All of these authors report successful reinduction in a certain percentage of cases many months, sometimes years, after pneumothorax had been purposely abandoned. The reason for the failure to reinduce the pneumothorax in those cases where rapid reexpansion has occurred (without treatment of the endobronchial lesion) is due to the fact that the lung is apposed to the chest wall under *positive* pressure and not because extensive pleural adhesions have obliterated the pleural space.

DISCUSSION

There is no substantiation for the concept that the loss of the pneumothorax space following a closed pneumonolysis is due to loss of air (mere escape) through the wounds made in the chest wall. The causal relationship has been misinterpreted and the cause has been mistaken for the effect.

Rapid reëxpansion or atelectasis following a closed pneumonolysis does not occur very often. But when it does, it offers a problem for prompt treatment, since in the case of reëxpansion a successful pneumothorax is lost and in the case of atelectasis the problem of the unexpandable lung will arise. Further, the lung that rapidly reëxpands presents the problem of substitute therapy with the chances of success diminished because of the resulting obstructive emphysema and the creation of tension cavities.

Routine bronchoscopy before the pneumonolysis is performed, with local treatment of the endobronchial lesion, stands out as the procedure of choice. It should carry a far greater chance of success than postoperative treatment.

We do not argue that there may not be other factors along with the endobronchial lesion that explain the various conditions that we have observed and described. Nor do we argue that all endobronchial lesions must be followed by

the same course, since the type of lesion, its location, the degree of occlusion, and the amount and character of the secretions are factors that must all be optimum. On the other hand, failure to see the lesion bronchoscopically does not rule out its existence, since lesions in the smaller bronchi will escape detection. Further, oedema and/or tenacious secretions may institute the same sequence of events as does a frank endobronchial lesion.

Greater use of bronchoscopy, particularly in pneumothorax patients showing any signs of "irregularity," will undoubtedly increase our knowledge concerning consequences that these lesions are capable of initiating.

Final proof will be obtained when a sufficient number of patients whose pneumonolysis is complicated by rapid reëxpansion or atelectasis receive treatment for their endobronchial lesions; for successful treatment will be followed by the ability to reinduce pneumothorax in the case of rapid reëxpansion and ability to reëxpand the lung in the case of atelectasis.

CONCLUSIONS

1. Endobronchial lesions, after a closed pneumonolysis, may produce a check-valve type of obstruction that results in rapid reëxpansion of the lung and loss of the pneumothorax space.
2. Under similar conditions, endobronchial lesions may cause complete occlusion that results in atelectasis.
3. Related conditions associated with pneumothorax therapy are explained on the basis of the formation of obstructive endobronchial lesions.
4. Therapy is suggested.

CONCLUSIONES

1. Las lesiones intrabronquiales, después de una neumolisis cerrada, pueden producir una obstrucción de tipo de válvula de retención que hace reexpandir rápidamente el pulmón y desaparecer el espacio dejado por el neumotórax.
2. En circunstancias semejantes, las lesiones intrabronquiales pueden provocar una oclusión total que culmina en atelectasia.
3. Ofrécese aquí una explicación de los estados afines asociados con la colapsoterapia tomando por base la formación de lesiones intrabronquiales obstructoras.
4. Bosquéjase la terapéutica.

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TRANSPLEURAL INTRACAVITARY ASPIRATION (MONALDI)[1,2]

Report of Three Cases

EUGENE J. DES AUTELS AND JOHN N. HAYES

A review of available literature (1 to 16) on the Monaldi procedure reveals a dearth of information concerning postoperative problems. We are presenting our limited experience in this period, hoping to stimulate more extensive discussion of this phase. The Monaldi procedure was employed in our cases primarily because it could be replaced by no other form of therapy. When a free pleural space near the proposed site of puncture was found preliminary to operation, symphysis was obtained by instillations of blood following the technique of Kupka (1). Preliminary roentgenological studies of the size, shape and location of cavities were done. The operations by Dr. Warriner Woodruff were performed under local anaesthesia; the exploratory needle, trochar and tube were easily and simply introduced into the cavities and intracavitary readings recorded. No operative difficulties or complications were encountered. The distances, as determined by manometric readings, from the skin to anterior wall of the cavity, from skin to its posterior wall and the depth at which the tube was left *in situ* were recorded at the operation.

THE WOUND

Wounds should be dressed frequently, especially during the first two weeks, and given the care of any similar wound. Discharge around the catheter was slight. Occasionally silver nitrate was used to control exuberant granulation tissue; wet boric-acid dressings were quickly efficient in controlling inflammation but were rarely necessary. The wounds tend to grow tightly around the tube and maintain air-tightness. This is necessary to avoid aspirating secondary organisms into the cavity; and to avoid a loss of suction pressure. At each dressing, the depth of the tube is checked and any change noted. In case 3, the tube was removed July 10, 1941 and the sinus closed and healed rapidly (see case report).

THE TUBE

The drainage tubes used were # 13 F. catheters with three eyes and marked off in centimetres. The position of the tube in relation to the cavity may be observed by periodic intracavitary manometric readings, fluoroscopy, anteroposterior and lateral X-ray films, planigraphy, instillations of contrast media and by noting any change in depth of the inlying tube. The tube is securely fastened to the chest to avoid accidental removal, yet leaving a free loop of the tube as it emerges at the skin to allow for slow gradual spontaneous expulsion as the cavity closes. Accidental dislodgment of the tube may occur, but, in our

[1] From Sanatorium Gabriels, Gabriels, New York.

[2] Presented before the Saranac Lake Medical Society, March 26, 1941.

experience, it has been easily replaced. Obstruction of the tube with drainage occurs very frequently, and may be indicated by failure to obtain intracavitary pressure readings, by dropping lipiodol into the tube or by failure to withdraw air on gentle suction with a syringe. If the obstruction is not removed easily by suction, one may irrigate through the tube with a small amount of sterile water.

REMOVAL OF TUBE

The literature indicates that in most cases the tube is gradually spontaneously expelled as the cavity closes, and that this occurs usually after three to six months. If the Monaldi operation proves unsuccessful after a trial of six months, Kupka[3] believes that further possibilities of success are minimal and that the procedure should be abandoned. None of our cases showed any tendency toward spontaneous expulsion after more than twelve months. We hesitate to remove the tubes in 2 cases, because we have no other therapy to offer these patients at this time. In one case the tube was removed and a thoracoplasty will soon be done.

TYPES OF SUCTION

Suction may be applied from various sources including a two-bottle siphon used by Monaldi, a motor or a water tap. Motor suction remains constant at a fixed figure. Water-tap suction varies somewhat as the flow of water varies. Suction originating from a bottle set-up changes as the differential of the two fluid levels changes; it starts from the original differential (for example, 30 cm. water) and, as the water levels approach each other, falls to zero. Monaldi thinks this variable suction allows the tissues, that may be injured by the greater negative pressures, an opportunity for recuperating during the periods of smaller negative pressures. This may be true and if so the water tap and motor do not have this advantage unless alternating values are introduced into the suction line. When the communicating bronchi of a cavity are widely patent, bottles may empty rapidly (for example, every five to ten minutes). This requires constant nursing supervision at a cost prohibitive to most patients, unless a nurse is assigned a group of patients for this duty alone. Water tap and motor suction avoid this work. Water-tap suction is generally available and least expensive. In the majority of cases reported, bottle suction was employed. With 2 patients we started with bottle suction but soon changed to water tap. One patient has had a motor pump.

DEFINITION OF SUCTION PRESSURE

Here we will insert a few arbitrary terms and definitions. All readings of manometric pressures and suction are made on the assumption that the set-up (figure 1) is completely air-tight. We consider *suction pressure* as that registered by a water manometer directly connected to the source of suction. The point (mercury valve) at which the pressure is broken and which limits the maximal

[3] Personal communication.

degree of suction is called the *valve-point pressure.* It is that point of negative pressure at which the safety valve allows room air to enter the suction line; it is recorded by a water manometer and by the depth the air-ingress tube is introduced into the mercury. When suction pressure is set above valve-point pressure the valve breaks the suction at valve-point pressure, protecting the lung from a potentially dangerous excessive suction. Intracavitary pressure means the actual suction pressure within the cavity as measured by a water manometer. Intracavitary pressure varies with the rate of egress and ingress of air from and to the cavity.

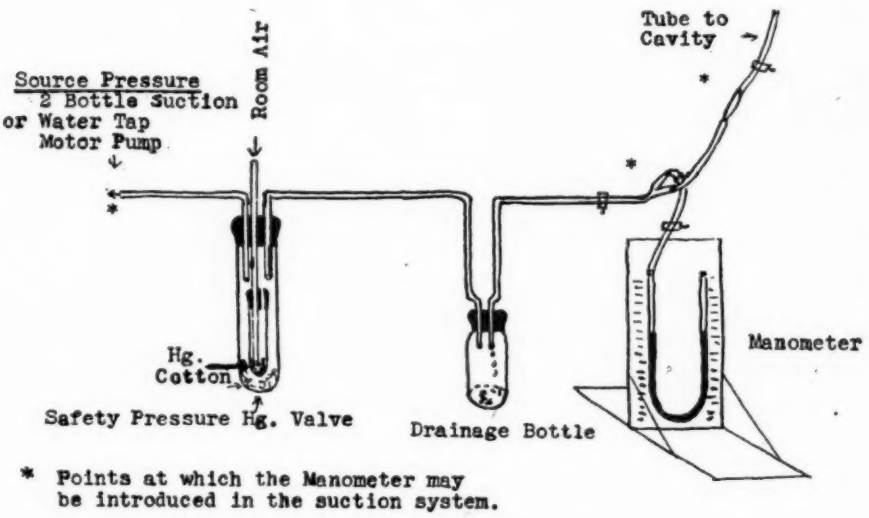

FIG. 1. Diagram of apparatus

FLOW OF AIR

Egress of air from the cavity varies with the (*1*) size, (*2*) location and (*3*) patency of the tube; (*4*) with the air-tightness of the set-up (leaks reduce the suction); (*5*) with the source pressure or water flow (the greater the source pressure or water flow, the more rapid the egress); (*6*) with valve-point pressure (egress would be greater at −30 cm. water than at −2 cm.); and (*7*) with the patency of the cavity and of its communicating bronchi. If the cavity and its bronchi were closed there would be no egress of air; whereas were they widely patent more air would be aspirated. Ingress of air into the cavity varies with the size of the lumina of the communicating bronchi. The bronchi will be discussed at greater length below. Finally, the more rapid the suction, the more air that may be aspirated into and through the cavity, via bronchi and via tube.

If the source pressure draws air much more rapidly from the cavity than air can enter it through the bronchi, the intracavitary pressure approaches valve-point pressure; and if egress of air is only slightly greater than ingress of air into the cavity, intracavitary pressure is less negative than valve-point

pressure. In the early course of case 3, employing water bottles with a differential in fluid levels of 50 cm. water, source pressure equaled −50 cm. water, while intracavitary pressure equaled −6 to −8 cm. water. Water flowed freely and continuously from bottle to bottle, emptying in five to seven minutes. Using water-tap suction with an intervening safety pressure valve at this same period, source pressure equaled −100 cm. water, valve-point pressure equaled −30 cm. water, intracavitary pressure equaled −15 to −20 cm. water. Six months later similar tests with bottle suction gave the following results: source pressure equaled −50 cm. water; intracavitary pressure equaled −45 to −48 cm. water. With water tap suction source pressure equaled −50 cm. water; valve-point pressure equaled −18 cm. water, intracavitary pressure equaled −17 to −18 cm. water. We interpret the above example as indicating a diminution of ingress of air into a reduced cavity because of its less patent bronchi at the time of this test. At this time the water in the two-bottle suction system flowed intermittently with his respiratory cycle, flowing during inspiration and stopping during expiration. This seemed to indicate that the bronchus or bronchi communicating with the cavity were open with inspiration and closed with expiration.

SUCTION PRESSURE

Suction should probably not be applied for the first twenty-four hours or as long as gross bleeding persists. Yet we did apply suction in our cases immediately after the operation with no complication. We have no doubt this is a dangerous policy to follow. Suction should generally be within the range of −15 to −30 cm. water with some variations allowable in the individual case. Most of the reports in the literature concern bottle suction, with a differential in fluid levels of 15 to 30 cm. water which we found may result in very small intracavitary pressure (for example, −4 to −10 cm. water in 2 of our cases); whereas we employed intracavitary pressure between −15 to −30 cm. water. Excessive suction may contribute to a number of complications enumerated in the literature. In one of our cases, excessive suction immediately postoperatively closed a cavity too suddenly, a homogenous shadow appeared in the surrounding area; this we interpreted as pulmonary engorgement with transudation into the alveoli. This cavity has since reopened. In another case (case 3) whenever intracavitary pressure exceeded −20 cm. water, unbearable pain occurred in the shoulder area.

CAVITY CHANGES

The progressive changes in cavities, following the Monaldi procedure, have been studied by cavernoscopy with photography (Davidson) (4) and by serial roentgenology with various positions and techniques including fluoroscopy and planigraphy. A close study of the cavity drainage gives us indispensable information concerning changes taking place within the cavity. Instillation of lipiodol (16) through the drainage tube may reveal residual sinuses, communicating bronchi or even residual cavities not seen on ordinary X-ray films or on

planigrams. Possibly, the positive pressure of the column of lipiodol, even though it is not forced into the catheter, may tend to distend a cavity or even separate approximated cavity walls that have not become adherent. Intracavitary readings are another source of information as to the condition of the cavity and its communicating bronchi.

BRONCHIAL PATENCY

The communicating bronchi have much to do with the ingress of air into a cavity. They vary in numbers, size and patency. Patency of the bronchi (16) varies with the mechanical effects of pathological lesions, with the presence or absence of valves and with the intermittent reduction or closure of their lumina by secretions. Bronchi enlarge during inspiration and decrease in size during expiration. Changes in position and movements of the patient influence the patency. The bronchial lumina also vary with the size of the cavity and with the intracavitary pressure; if suction reduces the size of the cavity it may simultaneously influence the patency of the bronchi.

We have a number of ways by which we may obtain information about the patency of the communicating bronchi. Instillation of lipiodol via the drainage tube will often reveal the residual cavity and its draining bronchus if the latter is sufficiently open. If lipiodol or dye is introduced into the cavity and quickly expectorated, the communicating bronchus or bronchi are open. We have confirmed the following studies reported by Davidson (4). Intracavitary readings tend toward the positive side when a check valve mechanism is present in the bronchus (for example, $-3, +7$ or $0, +7$); readings approach neutral with a widely patent bronchus (for example, $-4, +4$); and when the bronchus is occluded, air is absorbed from the cavity tending to result in negative readings (for example, $-6, -1$ or $-8, -1$). With the bronchus closed (4) and the drainage tube open if the patient expires forcefully and then the tube is clamped, intracavitary readings become more negative (for example, readings before this manoeuvre, $-4, -3$, after $-7, +0$); by repeating the manoeuvre but clamping the tube at the end of deep inspiration, readings become more positive (for example, $0+7$). If the bronchus is closed, and the patient (nose pinched) blows against a manometer while the drainage tube is just under the surface of a water trap, a few bubbles escape and then cease while the patient still maintains the blowing pressure on the manometer registering the oral pressure. If the bronchus is open during this manoeuvre, bubbles escape as long as patient maintains oral pressure on the manometer. Davidson (4) also differentiates between open and closed bronchi by variations of simultaneous manometric readings of intracavitary and intra-oral pressures. If the bronchus remains occluded negative intracavitary readings are maintained. Goldman *et al.* (16), introducing air into the cavity under positive pressures to give readings of $+10, +20$, then observed that intracavitary readings are maintained if the bronchus is closed and the check valves are 100 per cent competent; whereas, if the bronchus is open and the check valves are incompetent, the pressure will fall toward neutral readings. Patency of the bronchi may vary in all degress from complete closure to wide

patency and the same varies periodically which influences these tests in a corresponding manner. Cough and forceful inspiration or forceful expiration against a closed glottis also influence intracavitary readings. Davidson (4) says that the size of the cavity decreased on forced expiration when the drainage tube is under the surface of water, both with open and especially with closed bronchi. However, if the catheter is clamped and the bronchus closed, air cannot escape and cushions the cavity, keeping it open. Doubtless, someone may eventually report work on gas analyses of a cavity and its relation to cavities with open and closed bronchi. We have presented some tests on case 3 seeming to indicate opening and closing of bronchus during the respiratory cycle, after six months of cavity suction. The draining bronchi remain patent in cases 1 and 3. We note that the only case (case 2) in which the cavity may be closed and the sputum and drainage remain persistently negative is also the only case in which the communicating bronchi remain closed.

DRAINAGE

The drainage secretion in our cases varies in many characteristics, not only as changes occur within the cavity, but also with other factors. In 2 of our cases the amount was constantly 2 cc. In the third case, the amount decreased from 60 cc. early in the treatment, to about 20 cc. after three months, and remained about the same for many months. In this case the amount was increased (*a*) by increasing the intracavitary pressure (and vice versa); (*b*) when the bronchi were open (very little drainage occurred when the bronchi were closed); (*c*) with the onset of secondary infection. The character of the drainage was more purulent (*a*) during the early course of the treatment; (*b*) when secondary invaders appeared; (*c*) somewhat when intracavitary pressure was increased; and (*d*) during the morning when suction had been stopped at night. Although drainage became thinner in this case, it was not serous but rather it remained cloudy with secondary infection. The tubercle bacilli count dropped in all cases and is persistently negative in one case only. Secondary organisms appeared in ten days to three weeks and they persist. Cellular studies as well as the chemical analyses are interesting, but we have no extensive studies of them. When the drainage is thick and contains gross amounts of necrotic tissue, washing it out of the catheter will avoid more frequent plugging. Small amounts of gross blood appeared in the drainage during the fifth and sixth months of suction in 2 cases and was controlled by decreasing the suction pressures.

COMPLICATIONS

Complications in our cases were minimal. They were premature closure of a cavity in one case, later reopening; fleeting pulmonary transudation localized around the cavity in the same case; about 5 cc. of gross blood appeared in the drainage of 2 cases during the fifth and sixth months of suction treatment; one patient experienced pain in the ipsilateral chest on suction greater than -20 cm. water; and dry pleurisy occurred in the ipsilateral chest in one case four months after the Monaldi was done. More complications have been reported in the literature.

RESULTS

Results are not wholly satisfactory in our cases. All of the cavities are reduced in size but none is closed. Sputum is markedly decreased in quantity and bacillary count, but 2 are not persistently negative. Cough is much less in all. All our patients claim marked improvement in general well-being and show improvement in their general condition. Gain in weight occurred in all. In case 1 weight remained 98 to 100 pounds for one year before the Monaldi and is now 113 pounds. In case 3 the pulse rate persistently averaged 100 to 120 for more than five years prior to the Monaldi operation; it dropped to 68 to 74 within two months. This has been an interesting incident which has a possible relationship to the negative pressures induced within the thorax.

CASE REPORTS

Case 1: This is a twenty-seven year old white female who has had pulmonary tuberculosis for fourteen years. She has had a cavity in the right lung for three and a half years and a pneumothorax on the left side for four and a half years. This pneumothorax is inexpandible because of stenosis of the left main bronchus.

The family was X-rayed in 1927 because of contact and the patient's X-ray film revealed a minimal lesion of the left apex. She was admitted to a sanatorium for five months in 1929 and again for eleven months in 1931. During this time no cavity was seen. Her sputum remained persistently negative. In September, 1935, dry pleurisy developed on the right side and an X-ray film revealed a cavity on the left. Her sputum was now found to be positive. She was readmitted to the previous institution in January, 1936 and a pneumothorax was started on the left side.

She was admitted to Sanatorium Gabriels in January, 1938 with an effective 90 per cent collapse of the left side and a small cavity in the right apex which had appeared in February, 1937. Her sputum was Gaffky II. Six bronchoscopies were performed late in 1938 and early in 1939 because of marked bronchial stenosis of the left main bronchus. This occlusion became complete in spite of treatment. Gold therapy resulted in no benefit.

Collapse therapy on the right side was contraindicated because of the extremely limited pulmonary reserve as shown by repeated tests of the vital capacity and by bronchospirometry and because of a contralateral inexpandible lung. Refills are being continued on the left side to prevent severe toxic episodes which occur during our attempts at reëxpansion. Meanwhile, the cavity in the right apex enlarged and appeared to be diffusely adherent.

Preliminary to operation, the pleural space was found to be obliterated over the cavity area. Intracavitary aspiration was instituted on August 3, 1940 (figure 2). A very definite improvement in general condition was noted following the operation (chart 1). There was a marked reduction of cough and expectoration. The quantity of drainage remained constantly 2 cc. (c.f. Lit.). The bacillary content of the sputum and of the drainage diminished sharply but neither became persistently negative. During the year prior to operation her weight remained 98 to 100 pounds. Her present weight is 113 pounds.

The cavity could not be seen after eight hours of excessive suction (figure 3). This cavity reopened later. Although it remains reduced in size (figure 4), it has not changed materially since February, 1941. We encountered frequent plugging of the catheter by thick drainage, especially during the early postoperative period. This required frequent irrigations. After more than a year of suction treatment, the catheter still shows no

tendency toward spontaneous expulsion. Premature closure of the cavity (figure 3) occurred in this case due to excessive suction (chart 1). The diffuse shadow (figure 3) involving the cavity-bearing area was interpreted as engorgement and transudation due to excessive suction; although the possibility of atelectasis was also considered.

In November, 1940, three and a half months after operation, a dry pleurisy occurred on the ipsilateral side. This resolved in three weeks.

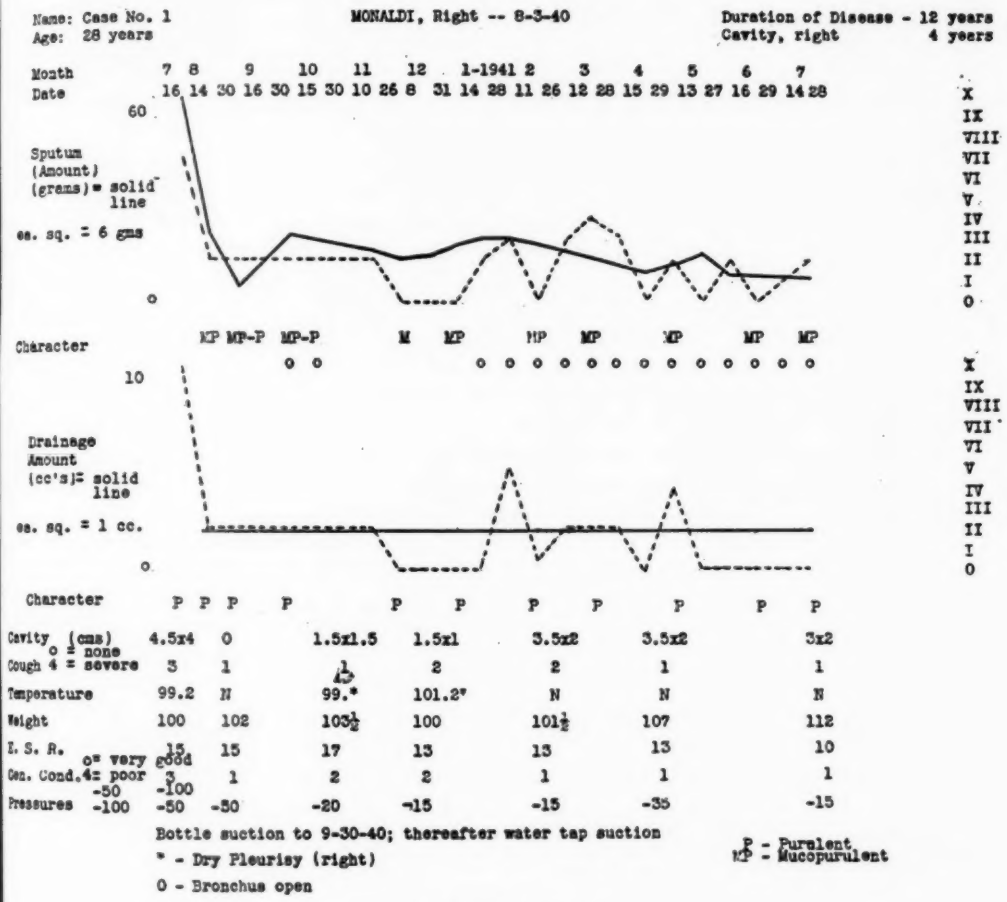
Name: Case No. 1
MONALDI, Right -- 8-3-40
Duration of Disease - 12 years
Age: 28 years
Cavity, right 4 years
Month 7 8 9 10 11 12 1-1941 2 3 4 5 6 7
Date 16 14 30 16 30 15 30 10 26 8 31 14 28 11 26 12 28 15 29 13 27 16 29 14 28
Sputum (Amount) (grams) = solid line
es. sq. = 6 gms
Character
Drainage Amount (cc's) = solid line
es. sq. = 1 cc.
Character
Cavity (cms)
Cough 4 = severe
Temperature
Weight
I. S. R.
Gen. Cond. 4 = poor
Pressures
Bottle suction to 9-30-40; thereafter water tap suction
* - Dry Pleurisy (right)
0 - Bronchus open
P - Purulent
MP - Mucopurulent
CAVITY = dotted line = CAVITY

CHART 1. Case 1

Thus, this case shows improvement and may be considered a partial but not a complete success.

Case 2: This is a thirty-three year old white male who has had pulmonary tuberculosis since 1935. He has had a cavity on the right side for five years and a bronchopleural fistula with mixed infection empyema on the left side for five years. He had a sudden pneumonic onset in May, 1935 with pleural effusion on the left side. He was admitted to a hospital on June 3, 1935 where aspiration was done once; a second tap in July, 1935 was dry.

He was admitted to Sanatorium Gabriels on August 13, 1935. On admission he was

very ill with a temperature of 103°F. and X-ray films revealed almost complete consolidation with a one-inch cavity on the left side; and a moderate amount of soft infiltration in the mid-lung field on the right side. Both apices were relatively clear. His sputum was positive.

His temperature remained 102° to 104°F. throughout the first ten months here. Meanwhile left pneumothorax was given October 13, 1935 and tension pneumothorax developed about six weeks later. No more refills were given. A pleural effusion appeared at this time and it contained tubercle bacilli. By late 1936 pyogenic organisms were also found in the pleural fluid. In January, 1937, a bronchopleural fistula was definitely demonstrated on this same side (left). The cavity disappeared with the onset of the tension pneumothorax, empyema and bronchopleural fistula and has not been seen since. Phrenic crush on the left side, April 8, 1936, was without effect. Thoracoplasty with Schede could not be employed because of the low vital capacity (40 per cent) and the extensive contralateral disease with a large apical cavity. Gold has been given in four courses (total 16.26 g. to date); during these courses he gained thirty pounds and he requests continuation of the gold treatment since he feels so much better with it.

His course subsequent to the empyema was marked by periods of exacerbation of infection in the left pleural space with inadequate drainage. Aspirations and irrigations with various solutions proved inadequate. Thoracotomy with tube drainage was done February 16, 1937. Temperature continued at a somewhat lower level (100° to 101°F.) until December, 1937. Thereafter his temperature remained nearly normal but was often 99.2°F. Daily irrigations were continued through the tube until November, 1938 (that is, twenty-one months); at this time the pleural space had become relatively dry and there was only slight discharge from the pleurocutaneous sinus. This continued for nearly a year; meanwhile the temperature remained normal.

An acute exacerbation of the pleural infection with a sharp rise in temperature occurred late in October, 1939; a thoracotomy with insertion of a drainage tube was done on November 11, 1939. Since this time palliative treatment, by daily irrigations using various antiseptic solutions, has limited the toxaemia and the temperature has remained normal (except for a two-day period in January, 1940 when drainage became inadequate and the infection was definitely worse).

Throughout this five-year period the cavity on the right side remained widely patent and the sputum averaged Gaffky III.

The Monaldi procedure was done for the large cavity on the right (figure 5) on August 22, 1940. After institution of this procedure the patient felt better (chart 2). His sputum was consistently Gaffky III for five years before operation. Since operation one to four bacilli were found on five examinations; fifty-one examinations have been negative and the last twenty-five consecutive sputa examinations have been negative. The drainage has never exceeded 2 to 5 cc.; the amount and its purulent character remain unchanged. Secondary infection has been aspirated across into the cavity area from the

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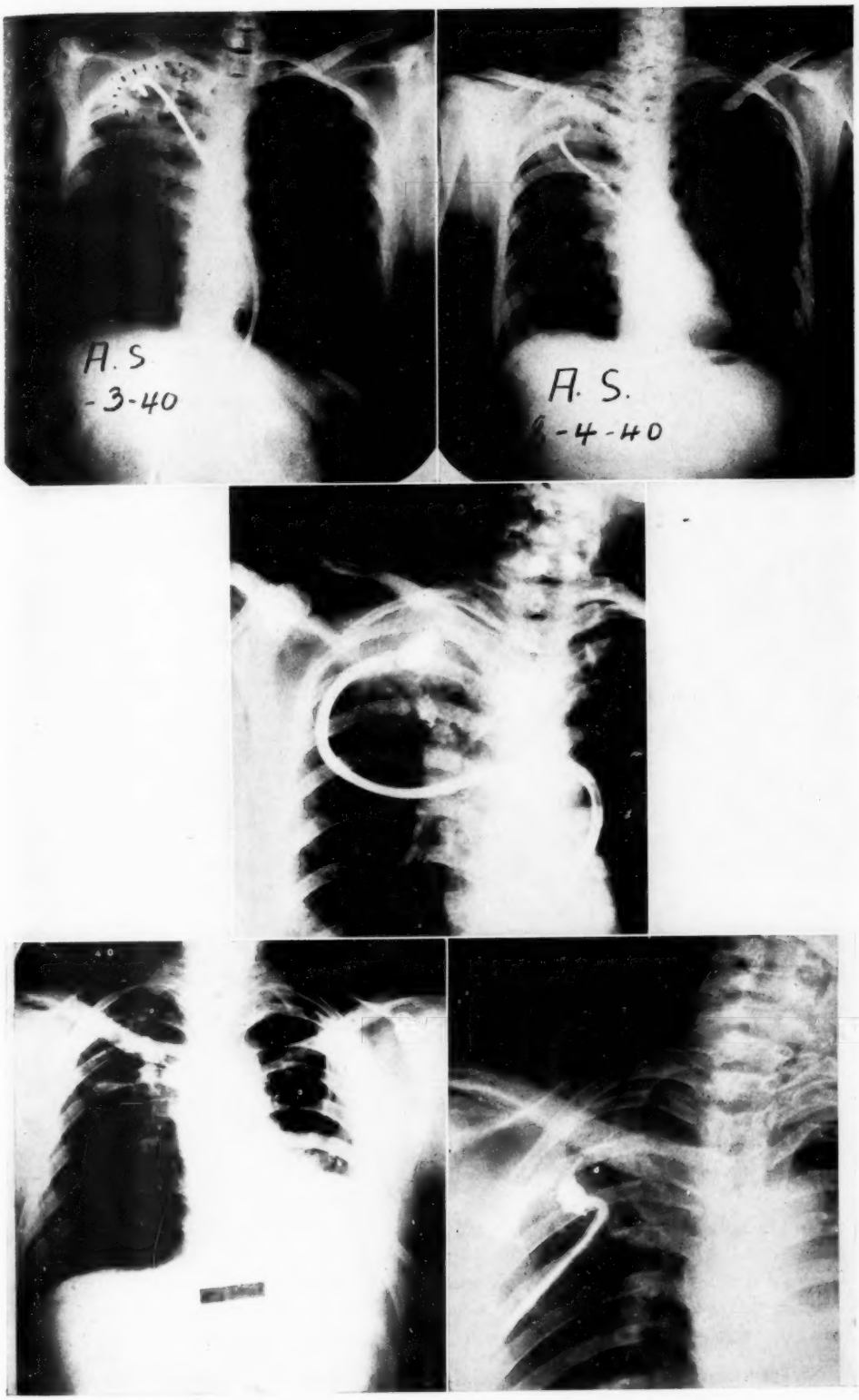
FIG. 2. Upper left (Case 1) August 3, 1940. Immediately after Monaldi.

FIG. 3. Upper right (Case 1) August 4, 1940. Cavity cannot be seen due to congestion from excessive suction.

FIG. 4. Center (Case 1) March 1, 1941. Lipiodol filling of cavity which was invisible on stereoscopic films. Some lipiodol visible in the draining bronchi.

FIG. 5. Lower left (Case 2) August 22, 1940. Before Monaldi. Right: Large cavity. Left: Partial collapse. Bronchopleural fistula. Thoracotomy.

FIG. 6. Lower right (Case 2) March 3, 1941. Lipiodol filling. Cavity could not be seen on stereoscopic films.



FIGS. 2-6

empyema of the contralateral side via its open bronchopleural fistula. This has been suggested by a predominating infection of *B. pyocaneous* both in the left pleural space and in the drainage from the cavity area of the right side under suction treatment. The tubercle bacilli content of the drainage dropped rapidly from Gaffky VII to none on the last forty-five specimens except for three bacilli seen after the tenth negative examination. The sputum and drainage have been persistently negative for more than eight months. The cavity has remarkably reduced in size; in fact it is not visible on ordinary X-ray films. Even lipiodol instillations (figure 6) suggest only a small residual cavity or possibly only a residual sinus in the cavity-bearing area. In this case, the communicating bronchi were closed on all tests and were not visualized with lipiodol instillation.

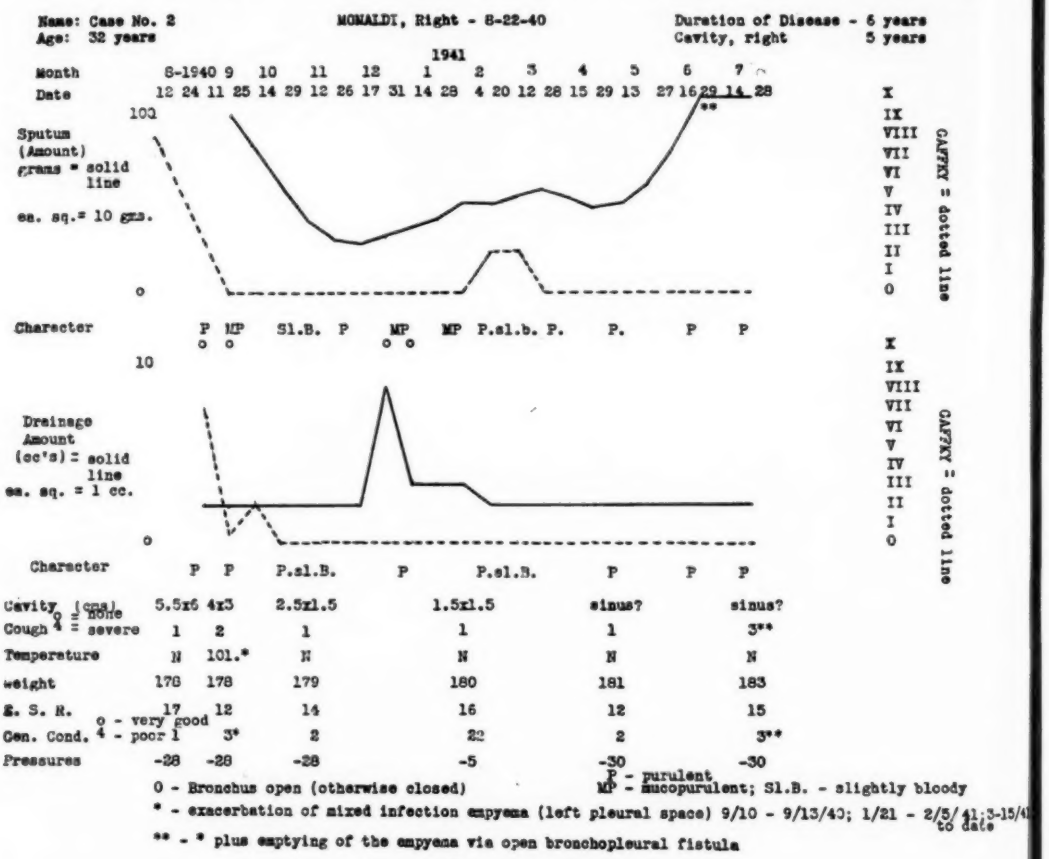

Name: Case No. 2
Age: 32 years
MONALDI, Right - 8-22-40
Duration of Disease - 6 years
Cavity, right 5 years
1941
Month 8-1940 9 10 11 12 1 2 3 4 5 6 7
Date 12 24 11 25 14 29 12 26 17 31 14 28 4 20 12 28 15 29 13 27 16 29 14 28
Sputum (Amount) grams = solid line
sq. = 10 gms.
GAFFKY = dotted line
Character P MP Sl.B. P MP MP P.sl.b. P. P. P P
Drainage Amount (cc's) = solid line
sq. = 1 cc.
Character P P P.sl.B. P P.sl.B. P P P
Cavity (cms) 5.5x6 4x3 2.5x1.5 1.5x1.5 sinus? sinus?
Cough 0 = none 4 = severe 1 2 1 1 1 3**
Temperature N 101.* N N N N
Weight 176 178 179 180 181 183
E. S. R. 17 12 14 16 12 15
Gen. Cond. 0 - very good 4 - poor 1 3* 2 22 2 3**
Pressures -28 -28 -28 -5 -30 -30
P - purulent
MP - mucopurulent; Sl.B. - slightly bloody
0 - Bronchus open (otherwise closed)
* - exacerbation of mixed infection empyema (left pleural space) 9/10 - 9/13/40; 1/21 - 2/5/41; 3-15/41 to date
** - * plus emptying of the empyema via open bronchopleural fistula

CHART 2. Case 2

In case 2 we have approached closure of a cavity and conversion of sputum but we are not certain until further time has elapsed. In this case, we realize the portent of the remaining mixed infection tuberculous empyema of the left side with an open bronchopleural fistula and the pleurocutaneous opening. Should we be able to bring the right side under proper control, we may also consider aggressive treatment of the left side. In any event, we consider the Monaldi as at least partially successful in this case.[4]

[4] The catheter was removed on October 11, 1941. The cavity was not apparent in December, 1941 but seen early in February, 1942, four months after removal of the catheter.

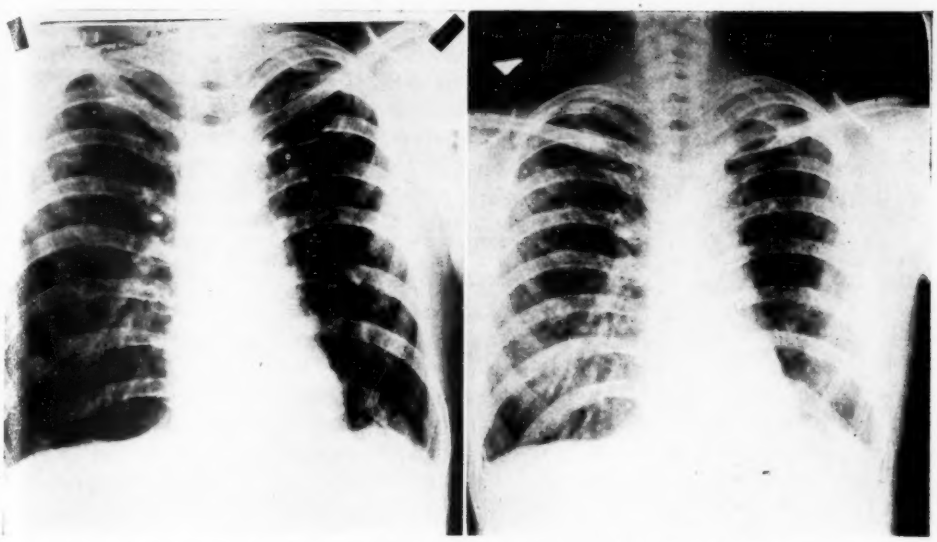


FIG. 7. Left (Case 3) 8–2–40 August 2, 1940. Before Monaldi. Right: Infiltration upper half. Left: Large cavity involving the apex to the second interspace.

FIG. 9. Right (Case 3) August 28, 1941. Left: Six weeks after removal of catheter, cavity reappeared.

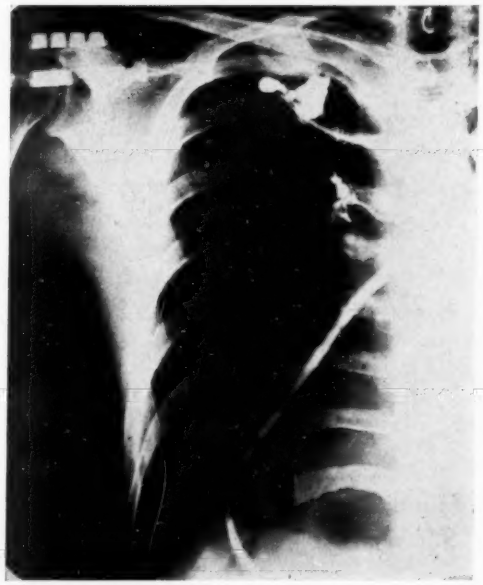


FIG. 8. (Case 3) May 27, 1941. Left lung only (film reversed in photography). Lipiodol filling of cavity which could not be seen on ordinary stereoscopic, bucky or planigraphic films. Several draining bronchi outlined.

Case 3: This is a thirty-year old white male who has had pulmonary tuberculosis for twelve years with a cavity on the left side for nine and a half years.

His onset was insidious about February, 1929. In October of that year he had a

haemoptysis with increase of symptoms and pain in the left chest. He remained in bed for nine days, returned to school and graduated January 20, 1930. His sputum was negative. He rested at home in the afternoons until February, 1932. Since he was not improving an X-ray film was taken and tuberculosis was diagnosed.

He was admitted to Sanatorium Gabriels February 19, 1932 with a moderate cough, no other symptoms and general condition good. An X-ray film taken on admission revealed a 3 cm. cavity in the right apex and a cavity in the left apex, measuring 3 by 2

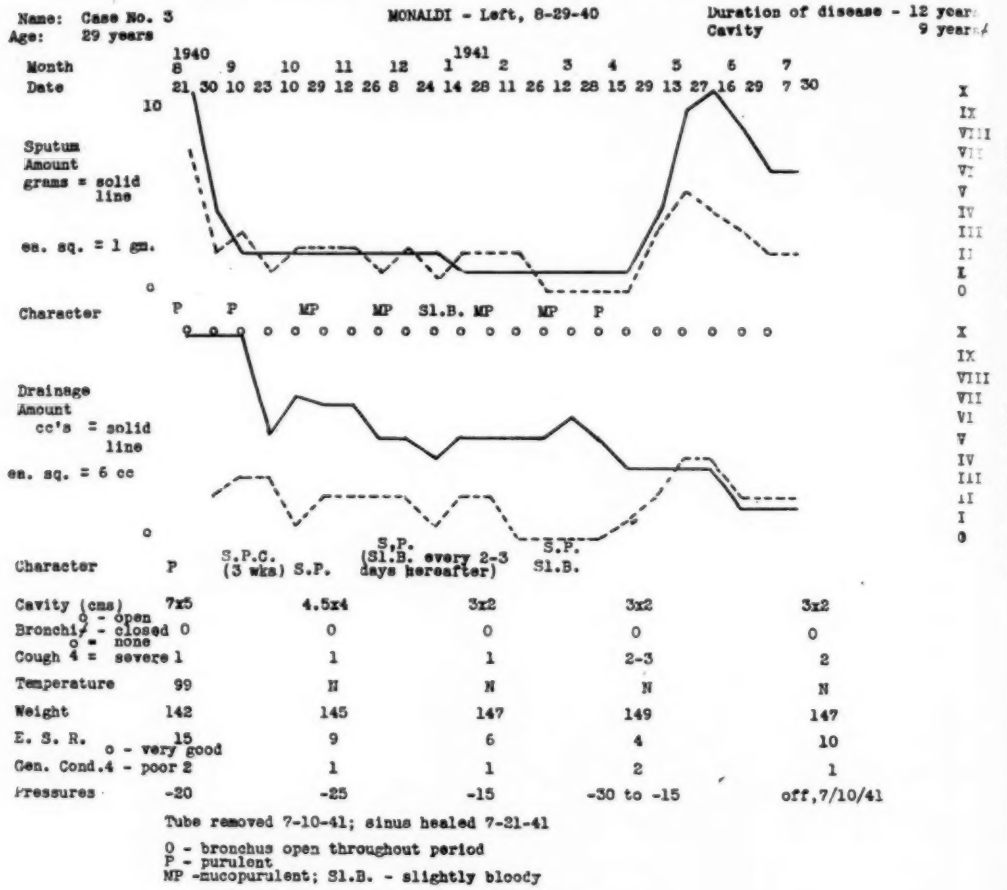

Name: Case No. 3
Age: 29 years
MONALDI - Left, 8-29-40
Duration of disease - 12 years
Cavity 9 years
1940
1941
Month 8 9 10 11 12 1 2 3 4 5 6 7
Date 21 30 10 23 10 29 12 26 8 24 14 28 11 26 12 28 15 29 13 27 16 29 7 30
Sputum Amount grams = solid line
sq. = 1 gm.
Character P P MP MP Sl.B. MP MP P
Drainage Amount cc's = solid line
sq. = 6 cc
GAFFKY = dotted line
Character P S.P.C. (3 wks) S.P. S.P. (Sl.B. every 2-3 days hereafter) S.P. Sl.B.
Cavity (cms) 7x5 4.5x4 3x2 3x2 3x2
Bronchi 0 - open 0 - closed 0 0 0 0 0
Cough 4 = severe 1 1 1 2-3 2
Temperature 99 N N N N
Weight 142 145 147 149 147
E. S. R. 15 9 6 4 10
Gen. Cond. 0 - very good 4 - poor 2 1 1 2 1
Pressures -20 -25 -15 -30 to -15 off, 7/10/41
Tube removed 7-10-41; sinus healed 7-21-41
0 - bronchus open throughout period
P - purulent
MP - mucopurulent; Sl.B. - slightly bloody

CHART 3. Case 3

inches, with extensive infiltration throughout both lungs. The cavity in the right side disappeared by June, 1934, reappeared in February, 1939 and closed again in July, 1940, not reopening to date. The cavity (figure 7) on the left has remained open and large since admission, that is, for more than nine and a half years. It is this cavity we subsequently attacked by intracavitary aspiration on August 29, 1940.

Except for short periods, prior to February, 1939, this patient remained partially ambulatory. Sputum analyses were persistently positive through these years, averaging Gaffky VII prior to the Monaldi procedure. Left pneumothorax was attempted in October, 1935 and was abandoned in December, 1935 as ineffective; it greatly embarrassed

the patient. One course of gold treatment was given from February to May, 1939 with subsequent slight improvement. A second course immediately affected the kidneys and necessitated cessation.

Before operation his vital capacity was 40 per cent and bronchospirometric studies revealed his respiratory function to be inadequate for thoracoplasty. Blood counts revealed a compensatory polycythaemia. For the five years prior to the Monaldi, his pulse was persistently 110 to 120 and it was uninfluenced by any therapy. Pleural symphysis was obtained by three instillations of the patient's own blood into the pleural space (10 cc. at weekly intervals).

Following cavity aspiration on August 29, 1940 we found in this patient that bottle aspiration was immediately unworkable because of the widely patent bronchus (figure 8) and rapid emptying of the bottles. When suction exceeded −20 cc. water, unbearable pain developed in the shoulder of the ipsilateral side.

This patient showed marked general improvement (chart 3) with a decrease of cough, expectoration and bacillary count, both of the sputum and the drainage. Although the cavity was greatly reduced in size, it remained open (figure 8) and the sputum remained positive in lesser numbers until May, 1941. In May, 1941, cough and expectoration increased and sputum became highly positive.

Almost immediately following removal of the tube on July 10, 1941, cough and expectoration became almost nil. This suggests that irritation from the inlying tube had been responsible for some of the increase of symptoms. The sinus closed and no drainage appeared after July 15, 1941.

In this case, the patient's general condition is greatly improved, the cavity is much smaller (figure 9), recent studies of the cardiorespiratory function show a decided improvement and he is now considered a fair risk for a subsequent thoracoplasty which will be done in the near future.[5]

SUMMARY

Postoperative care, observation and clinical course following Monaldi procedure are described. In 3 patients reported no complications occurred. The proper intracavitary position of the catheter is ascertained by manometric and X-ray observations. Suction is maintained by a motor or a water tap, producing an intracavitary pressure of between −15 to −30 cm. of water. Improvement in the patients' condition and decrease of the cavities were observed in all 3 patients, but in none did the cavity become closed.

SUMARIO

Descríbense la asistencia postoperatoria, observación y evolución clínica consecutiva al procedimiento de Monaldi en 3 enfermos, en ninguno de los cuales se notaron complicaciones. La posición intracavitaria de la sonda se averigua mediante la observación manométrica y roentgenológica. La succión se mantiene con un motor o grifo de agua, produciendo una presión intracavitaria de −15 a −30 cm. de agua. En los 3 enfermos mejoró el estado y disminuyeron las cavernas, pero en ninguno se cerraron éstas.

[5] Catheter was removed on July 10, 1941. Cavity reappeared on August 28, 1941. Two stages of thoracoplasty were done on September 10 and November 14, 1941, two ribs being removed each time. He died of respiratory failure on December 9, 1941.

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AMBULATORY PNEUMOTHORAX

Its Rôle in a Program of Treatment and Prevention of Tuberculosis

LEONARD B. GREENTREE[1]

LITERATURE

The tremendous cost of maintaining an adequate program for control of tuberculosis is almost an insurmountable obstacle for most nations with a limited national income. This can be readily understood when it is realized that the wealthiest of nations, the United States, still is some 20,000 beds short of the 120,000 beds deemed necessary for adequate control of tuberculosis. Clinical experience has shown that there should be two beds per annual death from tuberculosis (1). In the United States, about 60,000 persons die of tuberculosis annually; therefore, approximately 120,000 beds are required. Actually, there are 98,801 beds (2).

The average cost of hospitalization per bed in the United States is at least $1,200.00, not including initial construction cost (3). Thus, well over $100,000,000 can be estimated to be spent each year in the United States to care for about 420,000 (1) patients who have tuberculosis and for the one million members of their families who can be considered potential victims of tuberculosis. Although this tremendous amount is being spent, cities like Chicago, which has 1,800 beds for tuberculous patients and an estimated tuberculous population of 20,000, still need additional hospital facilities (4).

It is of interest to compare these figures with those for the Far East. It has been stated that there are two to five million cases of active tuberculosis in India alone (5). According to the Indian Medical Review of 1938 (6), in the Bombay Residency, which has the largest number of beds in proportion to the entire population, there is approximately one bed for 40,000 of population at large. In the Province of Assam, which has a population of more than nine million, there is not a single bed available for tuberculous patients. In the United States, there is on an average of one tuberculous bed for every 1,300 persons.

For a number of years a distinct and worthy effort has been made to fight tuberculosis in the Philippines, where the incidence of the disease varies from 6.25 (7) to 18.0 per cent (8). As the population is about sixteen million, there probably are about one million cases of tuberculosis. The death rate from tuberculosis in 1927 was 577.4 per 100,000 (9) as compared with a rate of 70 in the United States. Assuming that the death rate from tuberculosis has been reduced to 300, 96,000 beds still would be required to care for the tuberculous patients. Actually, slightly less than 1,000 beds are available. The entire revenue collected in the Philippines for the year 1939 was estimated to be $79,300,000 and the expenditures were $79,200,000. The revenue for the United States in the same year was $5,667,823,625 and the expenditures, $9,268,338,030 (10). Thus one can see that it is economically impossible for either India or the Philippines to hope ever to be able to institutionalize even a small fraction of the tuberculous patients. What has just been stated for these two countries also applies to a large percentage of countries with a limited income.

The results are apparent. The incidence of tuberculosis and also the mortality rate are increasing in Eastern Europe, the Balkan States, Spain, Central and South America, North and South Africa, India, China, the Malay States and the Philippines (9). One

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hesitates to think what further havoc the present world war will cause. These countries also are confronted by a great scarcity of physicians specially trained in modern methods of treatment and in dealing with the many aspects of tuberculosis.

Frimodt-Möller, Medical Commissioner for the Tuberculosis Association of India, said: "In a country such as India where a raising of the general standard of living is likely to take generations and where, at the same time, the disease is on the increase, and the facilities for institutional treatment constitute the merest fraction of the enormous numbers of tuberculous patients, the emphasis in the control of tuberculosis must of necessity be a campaign which concentrates all its efforts on striking at the real cause of the disease, which is only one, namely the source of the disease." (5). The chief source of infection is the *Mycobacterium tuberculosis* from the sputum of tuberculous patients.

Tice and Hruby (4) made a critical study of the results obtained with collapse therapy at the Chicago Municipal Tuberculosis Sanitarium and its affiliated clinics. Their results showed that conversion to negative sputum was obtained in 39.8 per cent of their patients who had received ambulatory pneumothorax. By combining ambulatory pneumothorax with collapse therapy in the Sanitarium, they were able to reduce the mortality rate to 28.6 per cent as against 60.7 per cent of those patients who had not received collapse therapy. In all of the 2,824 cases in which collapse therapy was employed, the patients had been observed for three or more months before the study was made. Pneumothorax was not attempted in 3,015 cases because of refusal, adhesions, non-coöperation, failure to return, disciplinary discharge and various other reasons. In 1,378 of 2,824 cases the collapse was produced by means of pneumothorax. In 94.1 per cent of all cases the patients had advanced tuberculosis.

In an effort to combat the source of infection in Porto Rico, which has one of the highest death rates from tuberculosis (283 per 100,000 population in 1929–1930 (9)), Morales, Pastor and their associates have employed ambulatory pneumothorax in 3,460 cases at the tuberculosis clinics of Porto Rico (11). In 33 per cent (1,130) of the cases in which ambulatory pneumothorax was used the sputum became negative. This compares favorably with the figure of 39.8 per cent reported by Tice and Hruby. As a result of ambulatory pneumothorax, the 5,000 immediate members of the families of the tuberculous patients with negative sputum (1,130) will now no longer be considered potential victims of tuberculosis.

It seems logical to draw the following conclusions:

1. Collapse therapy can be looked upon not only as an individual therapeutic measure, but as a public health procedure of great significance.

2. From an economic viewpoint, it will be impossible for most countries to hope to have enough beds to care for even a small fraction of the patients who require hospitalization because of active tuberculosis.

3. There is a great scarcity of physicians specially trained in modern methods of treatment of tuberculosis.

PROPOSED PLAN

Bearing these observations in mind, I have worked out a program which offers I believe, a practical solution of the existing problem. It is as follows:

A small pneumothorax clinic should be established in each village of a specified district. It should consist of a waiting room, a treatment room and a small ward containing two to four cots. The equipment should consist of one pneumothorax unit with spare parts, one sterilizer, one microscope, scales for weighing, charts

and so forth. The personnel should consist of either two nurses or a young physician and one nurse, and such servants as will be necessary.

To this clinic should come every three weeks an ambulant roentgenoscopic unit, having a specialist trained in tuberculosis in charge. This unit should cover a circumscribed area of about ten villages. The unit should remain at each clinic on an average of two days. During this time, the specialist should examine with the roentgenoscope all patients whom the resident members of the clinic have gathered since the last visit of the unit. The specialist should decide the disposition of each patient. He also should decide whether or not pneumothorax should be instituted. In cases in which pneumothorax is being employed he should examine the patients roentgenoscopically and decide whether the pneumothorax should be continued or the patient referred to the sanatorium for surgical collapse. At the end of two days, when the unit departs for the next village, the resident staff should assume the rôle of the departed specialist and induce pneumothorax when necessary. At the onset of the program, it may be best that the specialist administer the initial filling, but the resident staff soon will be expert in its own right. The technique of pneumothorax is not difficult, especially if one remembers the dictum "no negative oscillation, no injection." The chances of accident are small. Morales (11) reported that in 128,000 refills at the clinics there were 82 accidents and 5 deaths. In view of the number of lives saved by pneumothorax, I believe that one can discount these unfortunate deaths as being of minor importance.

The functions of the village tuberculosis clinic should be:

1: Induction of pneumothorax under supervision of the District Tuberculosis Physician.
2: Periodic examination of sputum for tubercle bacilli; the first examination should be made before the initial filling.
3: Periodic check of weight, pulse, temperature and sedimentation rates of patients under treatment.
4: Administration of medicine, that is, iron for secondary hypochromic anaemia and vitamins for avitaminosis.
5: Tuberculin tests on babies and children.
6: Survey of incidence of tuberculosis in the district.
7: Dissemination of instruction and hygiene by lecture and pamphlets.
8: Periodic visits to homes of patients.

In the cities the program should be slightly modified from that used in the villages. The number of clinics will depend upon the size of the city. In a large city, there should be several clinics similar to those in the villages. In addition, there should be a clinic containing a roentgenoscope with a specialist in charge. This clinic also should make microscopical examinations. The patient should make his periodic visits to his neighborhood clinic for pneumothorax. Once a month, he should report to the main clinic for roentgenoscopic examination by the chief physician, and for a check of the sputum. The results of these examinations should be forwarded to the staff of the neighborhood clinics. In all cases of suspected tuberculosis the patients should be examined at the roentgenoscopic clinic. If the roentgenoscopic findings are indicative of tuberculosis, the

sputum should be examined and the patient should be given a card and instructed to present it to the clinic which is closest to his residence. In this manner ambulatory pneumothorax can be brought home to the patient in the large city and one tuberculosis specialist and one roentgenoscope can be made to serve an entire city.

Equally important to the tuberculosis program is the establishment of headquarters in one of the existing sanatoria. This is the brain centre of the entire project. Here should be trained the specialists and the future members of the village clinics. The workers in the field should return to this hospital periodically for refresher courses. The beds in this and other sanatoria already built should be, for the large part, converted into beds for patients requiring surgical collapse. No further appropriations for sanatorium construction should be authorized until the work in the field is well established.

SUMMARY

I have outlined a program for prevention and treatment of tuberculosis whereby:

1. Ambulatory pneumothorax therapy is brought home to the tuberculous patient at a minimal cost.

2. The village clinic will become the spearhead of attack against the chief source of infection, the *Mycobacterium tuberculosis* in the sputum of tuberculous patients.

3. The tuberculosis specialist and his roentgenoscopic equipment are made available to serve an entire district instead of an isolated community.

4. The limited financial resources of most countries and the extremely small number of physicians specially trained in modern methods of treatment of tuberculosis will be able to combat tuberculosis in a much more effective manner than is possible under existing methods.

SUMARIO

Bosquéjase un plan para la profilaxia y tratamiento de la tuberculosis, conforme a estas bases:

1. Llévese al domicilio del tuberculoso a costo mínimo la colapsoterapia ambulante.

2. La clínica-aldea se convierte en la primera arma de ataque contra el principal foco infeccioso, el *Mycobacterium tuberculosis* del esputo de los tuberculosos.

3. Pónense así a servir a un distrito entero, en vez de una comunidad aislada, al tisiólogo y a su instalación roentgenoscópica.

4. Aun con los limitados recursos económicos de la mayor parte de los países, y el pequeñísimo número de médicos preparados, especialmente en los modernos métodos terapéuticos de la tuberculosis, podráse así combatir la tuberculosis mucho más eficazmente que lo que resulta posible con los métodos actuales.

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QUANTITATIVE STUDIES OF THE TUBERCULIN REACTION[1]

III. Tuberculin Sensitivity in Relation to Active Tuberculosis

MICHAEL L. FURCOLOW, BARBARA HEWELL AND WALDO E. NELSON

The application of a quantitative method of tuberculin testing, as reported in the first paper in this series (1), offered an opportunity to restudy the relationship of tuberculin sensitivity to active tuberculosis—a problem which has been studied by a number of investigators (2 to 15). The purpose of the present study was to determine if possible whether color or sex, and various clinical findings affect tuberculin sensitivity, and whether quantitative tuberculin testing could be of aid in prognosis. No attempt was made to follow the fluctuations of tuberculin sensitivity with time (6, 7, 10, 11, 12).

MATERIAL AND METHODS

The quantitative method used in this study is that previously described (1). The method consists of testing a group of individuals with a graduated series of increasing concentrations of Purified Protein Derivative of tuberculin (PPD). First, all the individuals in the group are tested with exceedingly small doses of PPD and those who do not have reactions to the first tests are retested with more concentrated doses four days later. This procedure is continued, step by step, eliminating the reactors and retesting the nonreactors with more concentrated doses, until all the individuals react or the largest dose in the graduated series is given.

The intracutaneous method, employing new syringes and needles, is used in all the tests. One-tenth cc. of the required dilution of PPD is injected into each forearm of each subject tested. The reactions are read and the measurements in mm. recorded at twenty-four, forty-eight and seventy-two hours. The term "positive reaction," as used in this paper, describes an area of oedema (induration) with a mean diameter of 5 mm. or more at the forty-eight hour reading.

This series of tests was performed by a so-called "double testing" procedure, that is, a test of a given concentration of tuberculin was made on one arm, and a simultaneous test using the next larger or more concentrated dose was made on the other arm. If there was no reaction to either of these tests the next two larger doses of tuberculin were injected in the same manner. If, however, at the forty-eight hour reading, there was an oedematous reaction measuring 10 mm. or more in mean diameter, no further tests were given. Whenever there was a reaction in which the oedema measured less than 10 mm. in mean diameter at the forty-eight hour reading, only the next larger dose of tuberculin was given to avoid any serious reactions due to overdosage. It should be noted that the criterion for elimination from further testing (10 mm. or more of oedema at forty-eight hours) was different from that for determining a positive reaction (5 mm. or more of oedema at forty-eight hours).

The tuberculin: Dilutions in physiological saline from a single lot of PPD (Number 98970), which was kept as a 2 per cent solution with 0.5 per cent phenol, were made as required within twenty-four hours of use. The PPD was obtained from Dr. Florence Seibert of the Henry Phipps Institute and its potency was standardized by her. Accurately graduated chemical glassware and pipettes were used. The dilutions were all made by one person.

[1] From the Division of Public Health Methods, National Institute of Health, U. S. Public Health Service, and the Children's Hospital Research Foundation, Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.

Schedule of dosage: The dosage schedule (see table 1) included ten concentrations of tuberculin, beginning with .000,000,000,01 mg. of PPD in 0.1 cc. of solution. Each successive dose increased tenfold in concentration so that the tenth test contained .01 mg. of PPD in 0.1 cc. Tests 1 and 2 were not employed in the present study.

Definition of terms: Testing a person in the manner outlined above determines the smallest dose of tuberculin PPD to which he reacts. A positive reaction to a given dose, therefore, determines what may be designated the *sensitivity level* of that individual. In order to determine the total number of persons who would react to any given dose, it is necessary to add the number of reactors to that dose and to all the smaller doses, since it can be assumed that those who react to any of the smaller doses would also react to a larger one. Therefore, the number of reactors at each dosage level was accumulated and the result designated the *accumulated number of reactors* to each test dose. When this

TABLE 1

Schedule of the doses of tuberculin used in the various tests

TEST NUMBER	DOSE OF PPD IN MG. IN 0.1 CC.
1	.000,000,000,01 (1/100 billionth)
2	.000,000,000,1 (1/10 billionth)
3	.000,000,001 (1/1 billionth)
4	.000,000,01 (1/100 millionth)
5	.000,000,1 (1/10 millionth)
6	.000,001 (1/1 millionth)
7	.000,01 (1/100 thousandth)
8	.000,1 (1/10 thousandth)
9	.001 (1/1 thousandth)
10	.01 (1/100th)

accumulated number is expressed as a percentage of the entire population the *accumulated percentage of reactors* to the various test doses of tuberculin is obtained. By plotting the accumulated percentage of reactors against dosage a curve is obtained which is designated the *sensitivity curve* for the population under discussion.

Population tested: The group tested was the entire population of a sanatorium in Ohio, and included 468 white and colored tuberculous adults ranging in age from fifteen to seventy years.

Interpretation of roentgenograms: Roentgenograms of the patients' chests were interpreted by Dr. H. K. Dunham and Dr. John S. Skavlem.[2] The lesions were classified in the usual categories: far advanced, moderately advanced, minimal, pleurisy and primary, on the basis of interpretation of the most recent roentgenogram; and as progressive, stationary and regressive on the basis of serial films. The type of lesion, pneumonic or fibroid, was also noted.

Clinical estimate: The medical staff of the sanatorium classified the patients under their care as improving, stationary or worse. The status of each patient was graded on the basis of the general course of his disease and temporary changes were discounted. Knowledge of the interpretation of the roentgenograms, of course, influenced the clinical evaluation.

Subdivision of the total group according to race, sex and clinical estimate, is shown in table 2 and chart 1. In both races a larger percentage of females than of males was

[2] The authors wish to thank Doctors Dunham and Skavlem for permission to use their interpretations of the roentgenograms.

considered to be improving. In both sexes a larger percentage of the colored than of the white patients was rated as worse.

Sedimentation index: Since the method used (modified Westergren) consists of observing the amount of fall of the red blood corpuscles over a period of one hour it is considered an index rather than a rate. The method consists in mixing 1.6 cc. of blood with 0.4 cc. of sodium citrate (3.7 per cent solution) and filling a Westergren tube exactly to the 200

TABLE 2

Distribution of 416 tuberculous patients, classified according to color, sex and clinical estimate

CLINICAL ESTIMATE	WHITE				COLORED			
	Male		Female		Male		Female	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Improving	43	28.1	69	54.8	22	29.7	27	42.9
Stationary	62	40.5	40	31.7	25	33.8	17	27.0
Worse	48	31.4	17	13.5	27	36.5	19	30.1
Total	153	100.0	126	100.0	74	100.0	63	100.0

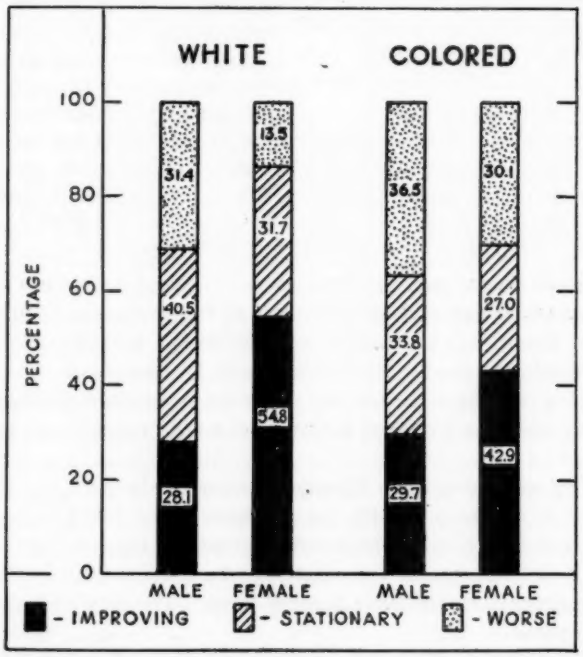

CHART 1. Distribution of 416 tuberculous patients, classified according to color, sex and clinical estimate.

mm. mark. The amount of fall, in mm., observed at the end of one hour is recorded as the sedimentation index. No corrections are made. The test is performed monthly on all patients.

Fever: Patients were classified according to temperature record as: normal, under 100°F., and over 100°F. for each of three periods—the month preceding the tests, the six months preceding the tests, and the time during which the tests were being made. An elevation of temperature was disregarded unless it persisted for more than two days.

RESULTS

For the total group of patients the number and percentage of reactors to the various test doses are shown in table 3 and the sensitivity curve is shown in chart 2. That members of the group are extremely sensitive to tuberculin may

TABLE 3

Number and percentage of reactors to the various test doses of tuberculin PPD among 468 tuberculous patients

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.	NUMBER POSITIVE	ACCUMULATED	
			Number	Per cent
1	.000,000,000,01 (1/100 billionth)			
2	.000,000,000,1 (1/10 billionth)			
3	.000,000,001 (1/1 billionth)	23	23	4.9
4	.000,000,01 (1/100 millionth)	32	55	11.8
5	.000,000,1 (1/10 millionth)	47	102	21.8
6	.000,001 (1/1 millionth)	148	250	53.4
7	.000,01 (1/100 thousandth)	142	392	83.8
8	.000,1 (1/10 thousandth)	74	466	99.6
9	.001 (1/1 thousandth)		466	99.6
10	.01 (1/100th)	2	468	100.0
Total		468		

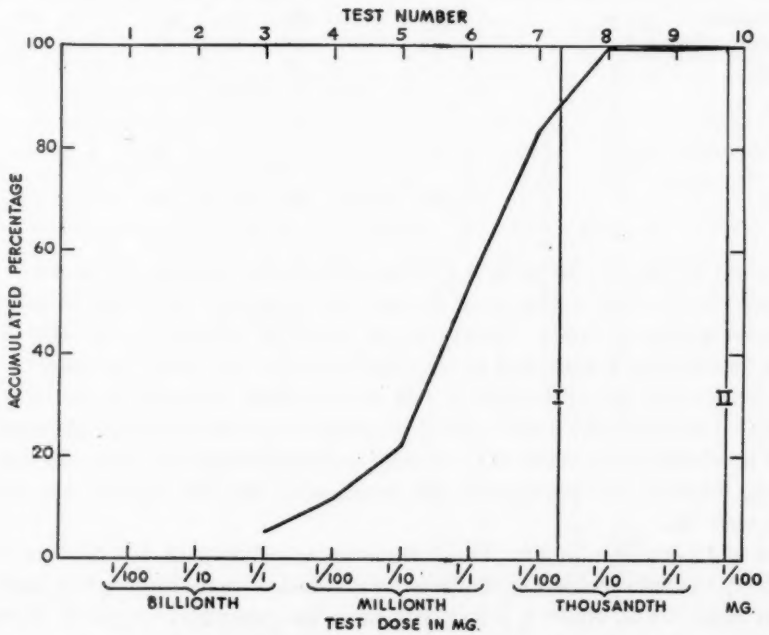

CHART 2. Accumulated percentages of reactors to various test doses of tuberculin PPD among 468 tuberculous patients aged fifteen to seventy years. The vertical lines, marked I and II, represent the approximate level of first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

be illustrated by the fact that 12 per cent react to test number 4, (.000,000,01 mg.), 84 per cent to number 7 (.000,01 mg.), and 99.6 per cent to number 8 (.000,1 mg.). Of the 468 patients only 2 failed to react to the last named dose. Both of these patients reacted to .01 mg. At the time of testing, both were very ill with tuberculosis and both died less than two months later. The results of the study indicate, therefore, that almost all persons with active tuberculosis react to low doses of tuberculin (.000,1 mg., or less, of the particular PPD used in this study).

The distribution of the test group by race, sex, and stage of disease is shown in table 4. While there were only 21 cases of minimal tuberculosis, their sensitivity curve was quite similar to the curves of those who had moderately advanced or far advanced tuberculosis. Only very slight differences in the sensitivity curves were observed when the total group was divided into age, race and sex groups or when classification was based on sedimentation indices for the previous six months or the most recently recorded index.

TABLE 4

Distribution of 468 tuberculous patients according to color, sex and stage of disease

STAGE OF TUBERCULOUS DISEASE	WHITE				COLORED			
	Male		Female		Male		Female	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Far advanced	154	88.0	88	64.7	61	72.6	50	68.5
Moderately advanced	13	7.4	35	25.7	11	13.1	10	13.7
Minimal	4	2.3	13	9.6	1	1.2	3	4.1
Pleurisy	4	2.3	—	—	4	4.8	10	13.7
Primary type	—	—	—	—	1	1.2	—	—
Extrapulmonary only	—	—	—	—	6	7.1	—	—
Total	175	100.0	136	100.0	84	100.0	73	100.0

Duration of disease: In table 5 the reactors to the various test doses of tuberculin are classified by duration of disease (by history). In chart 3, sensitivity curves are shown for only two groups of patients, namely, those who had the disease less than one year and those who had it for ten years or longer. Sensitivity curves for the other groups are intermediate between these two. Test number 7 (.000,01 mg.) may be used to exemplify the differences in sensitivity. At this level only 75 per cent of those who had the disease less than one year were positive, whereas the percentage for those who had the disease ten years or longer was 93.

Type of tuberculous lesion: The tuberculin sensitivity of patients having the fibroid type of tuberculosis is compared with that of those having the pneumonic type in table 6 and chart 4. Patients with the pneumonic type of disease are seen to be less sensitive than those with the fibroid type.

Roentgenological interpretation of the progress of the lesions: In table 7 are presented the number and percentage of reactors to the various test doses of tuberculin among patients whose lesions were classified as progressive, stationary or

TABLE 5

Number and percentage of reactors to the various test doses of tuberculin among 468 tuberculous patients, classified according to the duration of disease

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.	DURATION OF TUBERCULOSIS (YEARS)											
		Less than 1			1-4			5-9			10 and over		
		Number positive	Accumulated		Number positive	Accumulated		Number positive	Accumulated		Number positive	Accumulated	
			Number	Per cent		Number	Per cent		Number	Per cent		Number	Per cent
1	.000,000,000,01 (1/100 billionth)												
2	.000,000,000,1 (1/10 billionth)												
3	.000,000,001 (1/1 billionth)	6	6	4.6	9	9	4.5	5	5	6.2	3	3	5.4
4	.000,000,01 (1/100 millionth)	7	13	10.0	14	23	11.4	4	9	11.1	7	10	17.9
5	.000,000,1 (1/10 millionth)	8	21	16.2	21	44	21.9	13	22	27.2	5	15	26.8
6	.000,001 (1/1 millionth)	43	64	49.2	65	109	54.2	19	41	50.6	21	36	64.3
7	.000,01 (1/100 thousandth)	34	98	75.4	63	172	85.6	29	70	86.4	16	52	92.9
8	.000,1 (1/10 thousandth)	30	128	98.5	29	201	100.0	11	81	100.0	4	56	100.0
9	.001 (1/1 thousandth)	—	128	98.5	—	—	—	—	—	—	—	—	—
10	.01 (1/100th)	2	130	100.0	—	—	—	—	—	—	—	—	—
Total		130			201			81			56		

regressive on the basis of interpretation of roentgenograms. The differences in sensitivity (chart 5) may be illustrated by comparing for each group the percentage of reactors to test number 6 (.000,001 mg.). Only 29 per cent of those whose lesions were progressive reacted to this dose as compared with 56 per cent of those whose lesions were regressive.

Fever: In table 8 and chart 6 is compared the tuberculin sensitivity of those who had normal temperatures, temperature under 100°F., and temperature over 100°F. for the month prior to the time of the tuberculin testing. Sensitivity to tuberculin bore an inverse relation to fever, being highest for those with normal

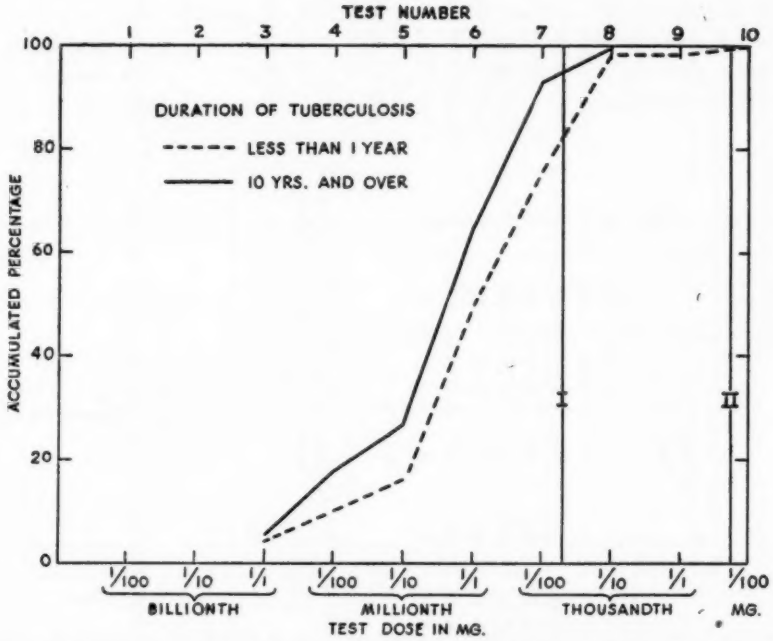

CHART 3. Accumulated percentages of reactors to various test doses of tuberculin PPD among 468 tuberculous patients classified by the duration of disease. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

temperature and lowest for those with temperature over 100°F. A similar situation was observed when the patients were classified according to their temperatures for the six months prior to the time of tuberculin testing.

Clinical evaluation: A comparison of the tuberculin sensitivity in patients whose clinical status was judged to be improving, stationary, or worse is found in table 9 and chart 7. Patients considered worse were less sensitive than those considered improving.

In table 10 and chart 8 are presented data on patients who died within six months after the tests and, for comparison, on those who survived. Those who died within this comparatively short time were much less sensitive to tuberculin than those who survived.

Sensitivity curve when 10 mm. or more of oedema is used as the criterion of a positive reaction: The results for the total group of tuberculous patients on whom this

TABLE 6

Number and percentage of reactors to the various test doses of tuberculin PPD among 421 tuberculous patients whose lesions were classified as either fibroid or pneumonic

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.	FIBROID			PNEUMONIC		
		Number positive	Accumulated		Number positive	Accumulated	
			Number	Per cent		Number	Per cent
1	.000,000,000,01 (1/100 billionth)						
2	.000,000,000,1 (1/10 billionth)						
3	.000,000,001 (1/1 billionth)	19	19	5.8	3	3	3.3
4	.000,000,01 (1/100 millionth)	24	43	13.0	5	8	8.8
5	.000,000,1 (1/10 millionth)	34	77	23.3	7	15	16.5
6	.000,001 (1/1 millionth)	108	185	56.1	23	38	41.8
7	.000,01 (1/100 thousandth)	101	286	86.7	30	68	74.7
8	.000,1 (1/10 thousandth)	44	330	100.0	21	89	97.8
9	.001 (1/1 thousandth)					89	97.8
10	.01 (1/100th)				2	91	100.0
Total		330			91		

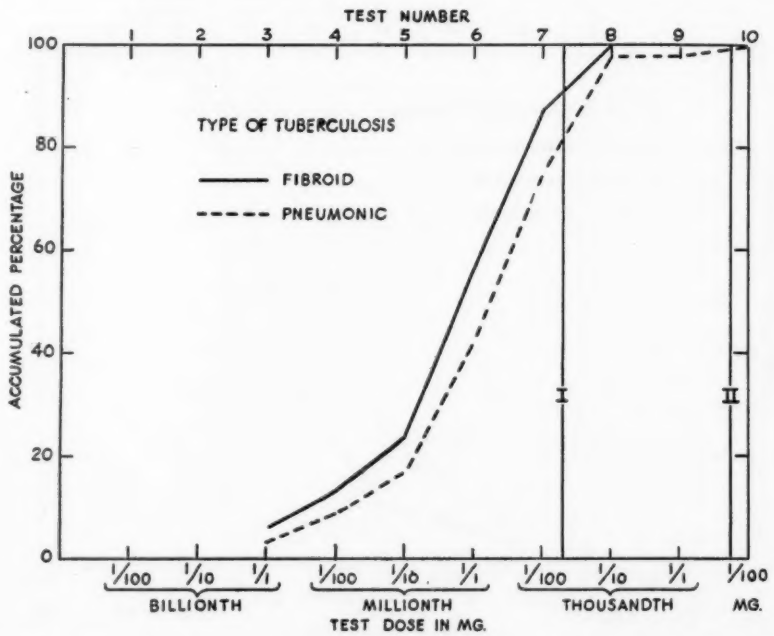

CHART 4. Accumulated percentages of reactors to various test doses of tuberculin PPD among 421 tuberculous patients whose lesions were classified as either fibroid or pneumonic. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

TABLE 7

Number and percentage of reactors to the various test doses of tuberculin PPD among 410 tuberculous patients classified according to the progress of their lesions as interpreted from roentgenograms

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.	ROENTGENOLOGICAL INTERPRETATION								
		Progressive			Stationary			Regressive		
		Number positive	Accumulated		Number positive	Accumulated		Number positive	Accumulated	
			Number	Per cent		Number	Per cent		Number	Per cent
1	.000,000,000,01 (1/100 billionth)									
2	.000,000,000,1 (1/10 billionth)									
3	.000,000,001 (1/1 billionth)	3	3	3.2	13	13	6.9	6	6	4.7
4	.000,000,01 (1/100 millionth)	4	7	7.5	12	25	13.3	15	21	16.3
5	.000,000,1 (1/10 millionth)	3	10	10.8	22	47	25.0	14	35	27.1
6	.000,001 (1/1 millionth)	17	27	29.0	73	120	63.8	37	72	55.8
7	.000,01 (1/100 thousandth)	39	66	71.0	50	170	90.4	39	111	86.1
8	.000,1 (1/10 thousandth)	26	92	98.9	18	188	100.0	18	129	100.0
9	.001 (1/1 thousandth)	—	92	98.9	—	—		—	—	
10	.01 (1/100th)	1	93	100.0						
Total		93			188			129		

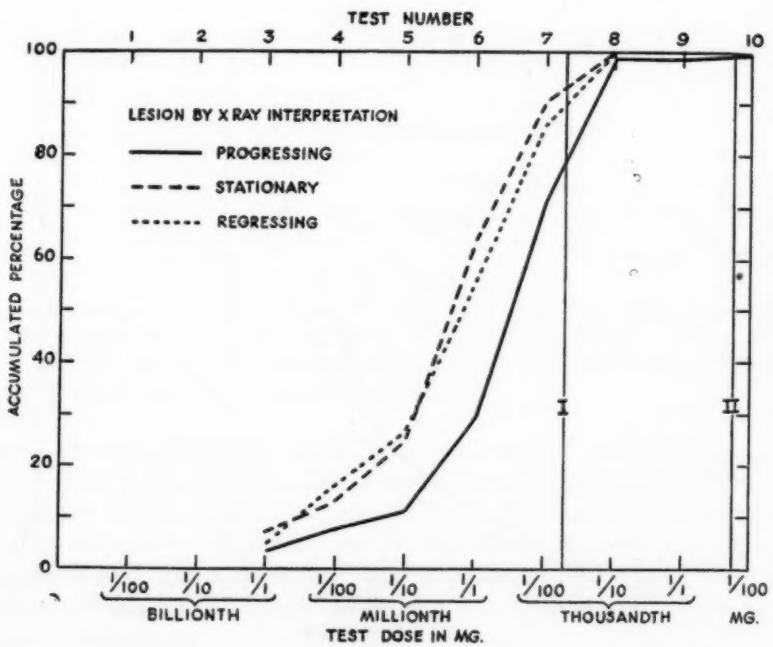

CHART 5. Accumulated percentages of reactors to various test doses of tuberculin PPD among 410 tuberculous patients whose lesions were classified as progressive, stationary or regressive as interpreted from roentgenograms. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

TABLE 8

Number and percentage of reactors to the various test doses of tuberculin PPD among 468 tuberculous patients, classified according to temperature record for the month preceding tuberculin testing

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.	NORMAL			BELOW 100° F.			ABOVE 100°F.		
		Number positive	Accumulated		Number positive	Accumulated		Number positive	Accumulated	
			Number	Per cent		Number	Per cent		Number	Per cent
1	.000,000,000,01 (1/100 billionth)									
2	.000,000,000,1 (1/10 billionth)									
3	.000,000,001 (1/1 billionth)	13	13	4.7	8	8	6.1	2	2	3.2
4	.000,000,01 (1/100 millionth)	22	35	12.8	7	15	11.5	3	5	7.9
5	.000,000,1 (1/10 millionth)	35	70	25.5	11	26	19.8	1	6	9.5
6	.000,001 (1/1 millionth)	95	165	60.2	41	67	51.1	12	18	28.6
7	.000,01 (1/100 thousandth)	77	242	88.3	47	114	87.0	18	36	57.1
8	.000,1 (1/10 thousandth)	32	274	100.0	17	131	100.0	25	61	96.8
9	.001 (1/1 thousandth)								61	96.8
10	.01 (1/100th)							2	63	100.0
Total		274			131			63		

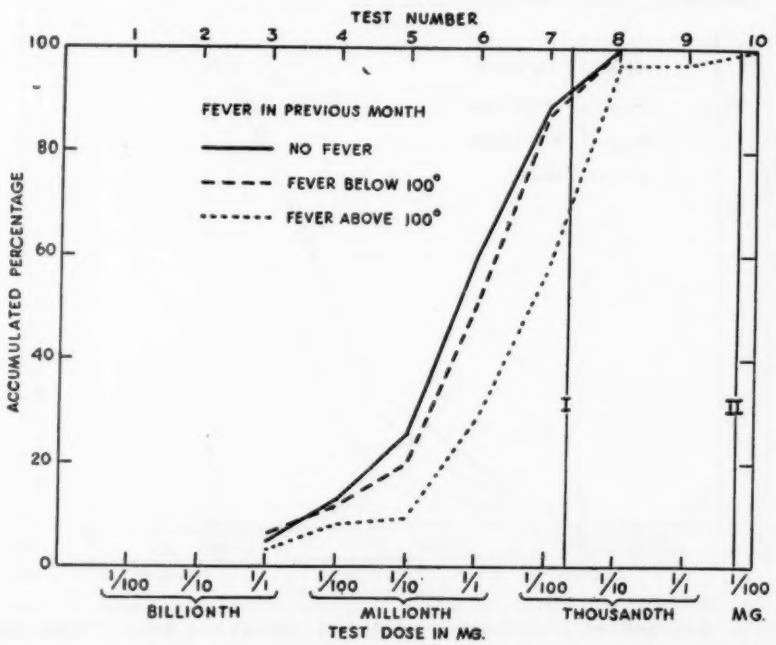

CHART 6. Accumulated percentages of reactors to various test doses of tuberculin PPD among 468 tuberculous patients classified according to temperature record for the month preceding tuberculin testing. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

TABLE 9

Number and percentage of reactors to the various doses of tuberculin PPD among 416 tuberculous patients classified according to clinical estimation

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.		IMPROVING			STATIONARY			WORSE		
			Number positive	Accumulated		Number positive	Accumulated		Number positive	Accumulated	
				Number	Per cent		Number	Per cent		Number	Per cent
1	.000,000,000,01	(1/100 billionth)									
2	.000,000,000,1	(1/10 billionth)									
3	.000,000,001	(1/1 billionth)	11	11	6.8	7	7	4.9	3	3	2.7
4	.000,000,01	(1/100 millionth)	16	27	16.8	10	17	11.8	4	7	6.3
5	.000,000,1	(1/10 millionth)	17	44	27.3	16	33	22.9	5	12	10.8
6	.000,001	(1/1 millionth)	48	92	57.1	55	88	61.1	28	40	36.0
7	.000,01	(1/100 thousandth)	47	139	86.3	44	132	91.7	39	79	71.2
8	.000,1	(1/10 thousandth)	22	161	100.0	12	144	100.0	30	109	98.2
9	.001	(1/1 thousandth)							—	109	98.2
10	.01	(1/100th)							2	111	100.0
Total			161			144			111		

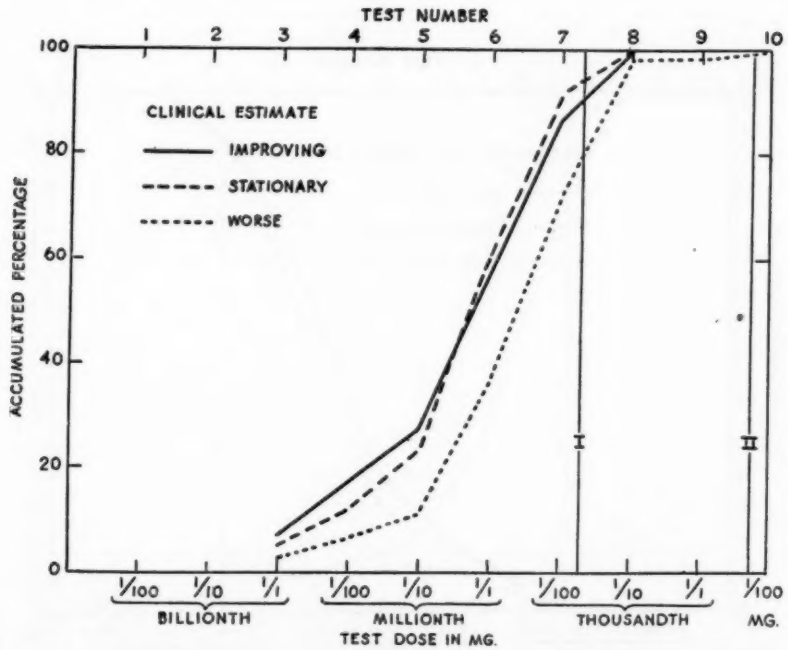

CHART 7. Accumulated percentages of reactors to various test doses of tuberculin PPD among 416 tuberculous patients classified by clinical estimation as improving, stationary or worse. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

TABLE 10

Number and percentage of reactors to the various test doses of tuberculin PPD among 468 tuberculous patients classified according to (1) those who died within six months of the beginning of the study and (2) those who survived this period

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.		(1) DEATHS			(2) SURVIVALS		
			Number positive	Accumulated		Number positive	Accumulated	
				Number	Per cent		Number	Per cent
1	.000,000,000,01	(1/100 billionth)						
2	.000,000,000,1	(1/10 billionth)						
3	.000,000,001	(1/1 billionth)	2	2	5.0	21	21	4.9
4	.000,000,01	(1/100 millionth)	2	4	10.0	30	51	11.9
5	.000,000,1	(1/10 millionth)	1	5	12.5	46	97	22.7
6	.000,001	(1/1 millionth)	7	12	30.0	141	238	55.6
7	.000,01	(1/100 thousandth)	10	22	55.0	132	370	86.4
8	.000,1	(1/10 thousandth)	16	38	95.0	58	428	100.0
9	.001	(1/1 thousandth)	0	38	95.0			
10	.01	(1/100th)	2	40	100.0			
Total			40			428		

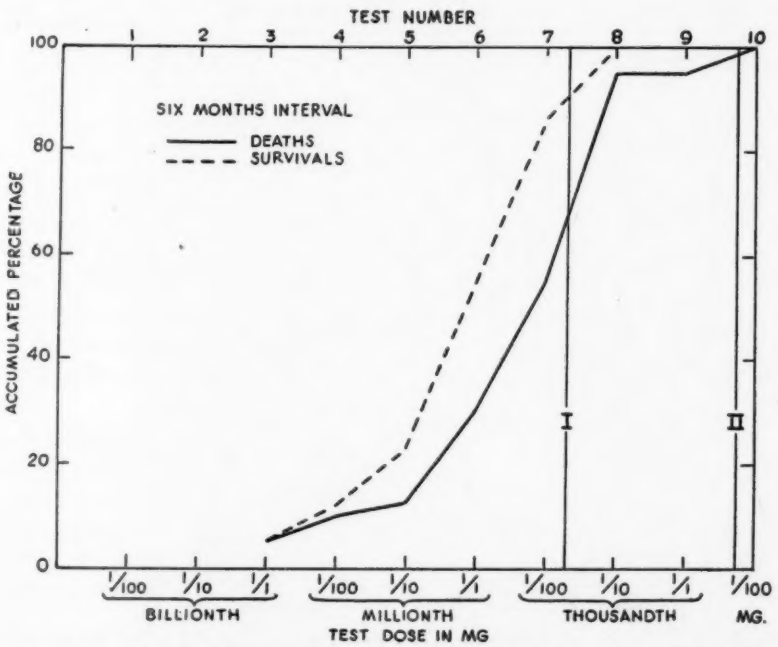

CHART 8. Comparison of the accumulated percentage of reactors to various test doses of tuberculin PPD between those who died within six months of the beginning of the study and those who survived this period. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

TABLE 11

Accumulated percentages of reactors for the same tuberculous patients when different criteria are used for describing a positive reaction

TEST NUMBER	TUBERCULIN PPD, TEST DOSE IN MG.	ACCUMULATED PERCENTAGE OF REACTORS WHEN	
		1	2
		5 mm. or more of oedema at 48 hours constitutes a positive reaction	10 mm. or more of oedema at 48 hours constitutes a positive reaction
1	.000,000,000,01 (1/100 billionth)	—	—
2	.000,000,000,1 (1/10 billionth)	—	—
3	.000,000,001 (1/1 billionth)	4.9	0.4
4	.000,000,01 (1/100 millionth)	11.8	2.4
5	.000,000,1 (1/10 millionth)	21.8	5.1
6	.000,001 (1/1 millionth)	53.4	20.5
7	.000,01 (1/100 thousandth)	83.8	65.1
8	.000,1 (1/10 thousandth)	99.6	99.3
9	.001 (1/1 thousandth)	99.6	99.6
10	.01 (1/100th)	100.0	100.0

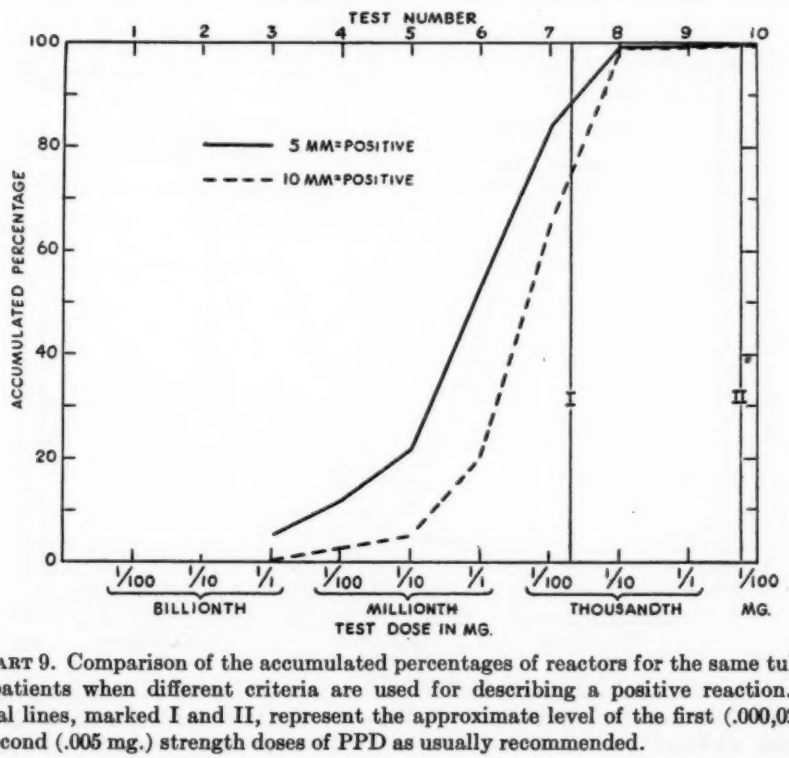

CHART 9. Comparison of the accumulated percentages of reactors for the same tuberculous patients when different criteria are used for describing a positive reaction. The vertical lines, marked I and II, represent the approximate level of the first (.000,02 mg.) and second (.005 mg.) strength doses of PPD as usually recommended.

information was available are presented in table 11. The *sensitivity curve*, using 10 mm. or more of oedema as the criterion of a positive reaction, is compared in

chart 9 with the *sensitivity curve* using 5 mm. or more of oedema as the criterion (chart 2). The forms of the two curves are quite similar; the differences which occur are among those who react to the less concentrated doses of tuberculin.

DISCUSSION

In general, it may be stated on the basis of the data presented that persons with active tuberculosis almost invariably react to low doses of tuberculin. There are, however, quantitative differences in the degree of sensitivity which seem to bear a relation to the severity of the disease. Patients who were most seriously ill were less sensitive or, in other words, required a greater quantity of tuberculin to elicit a positive reaction than did patients who had less serious disease and who appeared to be controlling their infection. Thus, short duration, pneumonic type of disease, progressive lesions, fever during the previous month or six months, and clinical estimation of failure to resist the disease, are all associated with decreased sensitivity to tuberculin. These findings may be interpreted to mean that the failure of bodily resistance resulting in progressive disease tends to reduce sensitivity to tuberculin as well as to produce fever, progressive lesions and so on. This point is illustrated by comparing the data for the 76 persons who were least sensitive to tuberculin with those for the remainder of the group (table 12). Seventy-four of these 76 persons reacted to test number 8 (.000,1 mg.) and 2 patients reacted to test number 10 (.01 mg.).

Table 12 shows that the portion of the group who were least sensitive to tuberculin contained a larger percentage of colored females and a larger percentage of younger persons (aged fifteen to twenty-four years) than did the remainder of the group. It is also evident that a much larger percentage of the least sensitive group had been fairly recently diseased (history of less than one year's duration). The percentage of patients that had temperature above 100°F. during the month previous to the study was four times as large in the group of 76 as in the remainder. In the least sensitive group the percentage that suffer from the pneumonic type of disease, have progressive lesions and are clinically worse, was twice as great as in the remainder of the group. In addition, the percentage that died within six months was four times as high in the least sensitive group as in the remainder.

While it is doubtful that information concerning the degree of sensitivity to tuberculin in persons with active tuberculosis is of very great practical value, it may be helpful in prognosis—especially when taken in conjunction with other clinical and laboratory data. Furthermore, it should be emphasized that the observations in this study were limited to persons with active tuberculosis. From a public health point of view, the practical value of these observations would appear to be that persons with active tuberculosis almost invariably react to relatively small doses of tuberculin, .000,1 mg. or less of the particular PPD used in this study. While it is shown that some loss of sensitivity to tuberculin may occur in the terminal stages of tuberculosis, it is significant that complete anergy was not found even in the most seriously ill patients in the group.

The question of the possibility of danger from tuberculin tests in patients with

TABLE 12

Comparison of the portion of the group who were least sensitive to tuberculin, with the remainder of the group

GROUP	COLOR AND SEX								TOTAL	
	White				Colored					
	Male		Female		Male		Female			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Least sensitive group....	25	32.9	22	28.9	11	14.5	18	23.7	76	100.0
Remainder of group.....	150	38.3	114	29.1	73	18.6	55	14.0	392	100.0
	AGE IN YEARS									
	15–24		25–34		35–44		45 and over			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
Least sensitive group....	25	32.9	20	26.3	19	25.0	12	15.8	76	100.0
Remainder of group.....	84	21.8	120	31.1	85	22.0	97	25.1	386	100.0
	DURATION OF TUBERCULOSIS (YEARS)									
	Less than 1		1–4		5–9		10 and over			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
Least sensitive group....	32	42.1	29	38.2	11	14.5	4	5.3	76	100.0
Remainder of group.....	98	25.0	172	43.9	70	17.9	52	13.3	392	100.0
	FEVER PREVIOUS MONTH									
	None		Below 100°		Above 100°					
	Number	Per cent	Number	Per cent	Number	Per cent				
Least sensitive group....	31	41.3	17	22.7	27	36.0			75	100.0
Remainder of group.....	243	61.8	114	29.0	36	9.2			393	100.0
	X-RAY DIAGNOSIS OF TYPE OF LESION									
	Chronic Fibroid		Pneumonic		Others					
	Number	Per cent	Number	Per cent	Number	Per cent				
Least sensitive group....	45	59.2	26	34.2	5	6.6			76	100.0
Remainder of group.....	285	72.7	65	16.6	42	10.7			392	100.0
	PROGRESS OF LESIONS ACCORDING TO X-RAY									
	Regressive (improving)		Stationary		Progressive					
	Number	Per cent	Number	Per cent	Number	Per cent				
Least sensitive group....	18	28.6	18	28.6	27	42.9			63	100.0
Remainder of group.....	111	32.0	170	49.0	66	19.0			347	100.0

TABLE 12—*Concluded*

GROUP	CLINICAL ESTIMATION OF STATUS OF PATIENT						TOTAL	
	Improving		Stationary		Worse			
	Number	Per cent	Number	Per cent	Number	Per cent		
Least sensitive group....	24	33.8	15	21.1	32	45.1	71	100.0
Remainder of group.....	137	39.7	129	37.4	79	22.9	345	100.0
	DEATHS IN 6 MONTHS SINCE STUDY							
	Number			Per cent				
Least sensitive group....	18			23.7			76	100.0
Remainder of group.....	22			5.6			392	100.0

active tuberculosis is frequently raised. It is obvious that care should be taken to prevent overdosage, and initial injections should be made with dilute solutions. In this series all persons were eliminated from further testing whenever they had a reaction in which the area of induration had a mean diameter greater than 10 mm. No ill effects were observed that could be attributed to the tuberculin reaction. During the study period 1.7 per cent of the patients had higher temperatures than during the preceding months, but more than five times that proportion had lower temperatures. We have no data on the possible harmful effect, in persons with active tuberculosis, of giving doses of tuberculin in excess of the sensitivity level.

SUMMARY

Of 468 tuberculous patients 99.6 per cent had positive reactions to a dose of .000,1 mg. or less of the particular PPD used in this study. Complete anergy to tuberculin was not encountered in the group.

Quantitative differences in the degree of sensitivity to tuberculin were observed. These differences appear to bear an inverse relation to the severity of the tuberculous infection.

The percentage of patients who died within six months following the study was four times as great among those least sensitive to tuberculin as among the remainder.

SUMARIO

De 468 tuberculosos, 99.6 por ciento resultaron positivos a una dosis de 0.0001 mg. o menos de la PPD utilizada en este estudio. En el grupo no se observó anergia completa a la tuberculina.

Observáronse diferencias cuantitativas en la sensibilidad a la tuberculina, las cuales parecen guardar relación inversa a la gravedad de la infección tuberculosa.

El porcentaje de enfermos que murieron dentro de seis meses después del estudio fué cuatro veces mayor entre los más sensibles a la tuberculina que en el resto.

The authors wish to express their appreciation to Dr. John S. Skavlem and the entire staff of the Hamilton County Tuberculosis Hospital for their willing coöperation.

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JAUNDICE IN TUBERCULOSIS

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Jaundice occurs rarely in tuberculosis. When it occurs, it may be caused by either extra- or intrahepatic obstruction. If extrahepatic, it may be due to tuberculous lymph nodes in the portal fissure pressing upon the bile ducts. Usually this is secondary to infection in the gastro-intestinal tract, carried by the portal circulation to the liver, and then through the efferent lymphatics from the liver to the nodes in the portal fissure. This is an unusual condition. Rare, too, is primary tuberculosis of the gallbladder. Latronche (1) mentions jaundice being present in one of his reported cases. Walters and Church (2) and Rankin and Massie (3) report incidences of the disease without jaundice and the latter authors report 15 authenticated cases in the literature.

The intrahepatic, toxaemic or haemohepatogenous type of jaundice occurs where there is tuberculosis of the liver itself and this is seen in: solitary tubercle, miliary tubercles or tuberculous cirrhosis.

Solitary tubercle, conglomerate tubercle or tuberculomata are comparatively large caseous masses which are found in the liver and, according to White (4), before they break down may be mistaken for nodules of lumphadenoma. They undergo caseation, soften and at times, when situated near the bile ducts, rupture into them leaving cavities in the liver. Solitary tubercles, in whatever form they appear, are a rare type of tuberculosis of the liver. Rolleston (5), in discussing bile duct tuberculosis, states that it is remarkable that jaundice is constantly absent, inasmuch as there is definite obstruction in some of the bile ducts. Bristowe (6) found 12 such cases of solitary tubercle with cavity formation in 167 cases of tuberculous ulceration of the intestines, but he does not mention the presence of jaundice. Thayer (7) reported a case of tuberculous cavities of the liver which showed jaundice for a week but which disappeared before death. Warthin (8) observed a case of bile-duct tuberculosis which had intense jaundice for three months preceding death. These solitary tubercles may, at times, become secondarily infected with pyogenic micoörganisms, soften and form single or multiple abscesses. Mayo-Robson (9) cites such an instance which came to operation and made a recovery. For three months prior to operation this patient had slight jaundice. A review of the literature shows that jaundice is rare in this type of tuberculous infection.

The experience of Warthin (8) is not confirmed by other observers when he states that 80 per cent of his acute general miliary tuberculosis of the typhoid form showed a variable degree of jaundice, and the same percentage of his cases of chronic tuberculosis, ending in a general miliary metastasis, showed the same occurrence of jaundice in proportion to liver involvement. Rolleston (5) remarks "although miliary tubercles in the liver are common, jaundice is rare." In 570 autopsies at the Henry Phipps Institute there was only one case of jaundice

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caused by miliary tuberculosis of the liver and, according to Cruice (10), only 7 cases of jaundice due to tuberculosis reported from the establishment of the institute until February, 1912 and 1,748 cases were hospitalized. Jaundice, when it occurs in miliary tuberculosis, is the result of a sudden unloading of innumerable organisms from a primary focus to disseminate throughout the liver with an obstruction of the intraäcinar bile capillaries. The infrequency of icterus shows that no absolute relationship exists between the degree of liver involvement and the occurrence of jaundice. In discussing the sources of origin for such spreads in miliary tuberculosis, Schmorl (11) listed vascular foci in 95 per cent of his cases; 50 involved the thoracic duct, 39 pulmonary veins, 3 right heart, 9 aorta and pulmonary artery and 16, other veins. Rolleston and McNee (12) cite the following as paths by which tubercle bacilli may reach the liver in such a spread: (*a*) the umbilical vein, (*b*) the hepatic artery, (*c*) the portal vein, (*d*) the lymphatics and (*e*) the common duct.

Transmission by the umbilical vein occurs during foetal life if there is tuberculosis of the placenta. The pathway in generalized tuberculosis is through the hepatic artery, although in some instances bacilli may enter the general circulation and generalized tuberculosis may not follow but miliary tubercles may be scattered through the liver, both inside the lobules and in the portal spaces. Recurrent attacks of such bacteraemia with tubercles of varying ages in the organs of the body are the basis for the chronic miliary tuberculosis noted by Hoyle and Vaizey (13). These authors further believe that the bovine rather than the human strain of tubercle bacillus may be the factor in chronic miliary tuberculosis. Fishberg (14) uses the duration of the process to classify the acute and chronic miliary tuberculoses: acute, 4 to 8 weeks; chronic, 2 months to a number of years.

In tuberculous ulceration of the intestine, tubercle bacilli may pass through the mucous membrane of the intestine without any gross lesion and then readily pass through the portal vein to the liver. In this condition acute miliary tuberculosis of an organ, such as the liver, may occur without a generalized spread. This was noted by Randolph (15).

In tuberculous peritonitis bacilli may possibly pass through the lymphatic vessels of the capsule into the liver. It is also conceivable that tuberculosis of the lymph nodes in the portal fissure, secondary to intestinal disease, might extend to the liver parenchyma against the lumph current.

It has been suggested that tubercle bacilli from the duodenum could pass up the bile ducts, work their way through the mucous membrane of the ducts into the portal spaces and there give rise to tubercle formation. In my opinion, Sergent's (16) work disproved this last possibility.

Regardless of the pathway by which bacilli may be carried to the liver, miliary tuberculosis as a disease occurs more frequently than solitary tubercle of the liver or primary tuberculosis of the gallbladder, but even in this condition the incidence of icterus is rare.

Tuberculous cirrhosis of the liver is a much debated entity. Hutinel (17), in 1881, observed large fatty livers in patients with active pulmonary tuberculosis.

Beauvy and Marré (18) found well marked fatty changes in the liver of an infant who died of miliary tuberculosis. Kaufmann (19) says that cirrhosis of the liver on a tuberculous foundation corresponds mostly to the picture of Laennec's cirrhosis. Kirch (20) believes that 4 of the cases mentioned in the literature as tuberculous cirrhosis of the liver are definitely proved, and further believes the condition possible, with its beginning in an interacinar tuberculous granulation tissue. Lorentz (21) found tuberculosis mentioned as the chief finding in 16 of 111 cases of cirrhosis of the liver. Hanot and Gilbert (22) describe a large fatty liver with small cell infiltration and fibrous hyperplasia of the portal spaces due to tuberculosis, which they call "hypertrophic fatty tuberculous hepatitis." Gougerot (23) produced a progressive fibrosis of the liver in guinea pigs by the use of tubercle bacilli. Isaac (24) states there is no doubt of the tuberculous aetiology of the cirrhosis which he describes as "a recent progressing atrophic or Laennec's cirrhosis with compensatory hypertrophy and fatty infiltration; also a tuberculous infection of the organ which is not recognized macroscopically. The cirrhosis does not distinguish itself grossly from the alcoholic cirrhosis." Kern and Gold (25) have been especially prominent in according to tuberculosis a rôle second in importance only to alcoholism in the causation of hepatic cirrhosis. Levinson and Karsner (26) state, "we therefore conclude that tuberculosis is one of the prominent factors in their causation" (cirrhoses). Contrary opinions are just as numerous. Ullom (27) says, "cirrhosis of the liver may accompany tuberculosis and be due to an entirely different cause." Rolleston and McNee (12) say "from a pathological point of view, tuberculosis, both in the liver, and when confined to some other part of the body, may, in certain circumstances, set up some fibrosis in the liver. There is no reason to think that genuine cirrhosis of clinical importance is primarily produced in this way. Tuberculosis, whether in the liver or elsewhere, may produce degenerative changes in the liver cells and, when there is preëxisting cirrhosis, considerable damage may be done in this way." The same authors conclude that tuberculosis elsewhere in the body may lead to changes in the liver: first, by focal and coagulation necroses due to the virulent action of bacilli on the liver cells—this was experimentally studied by Pilliet (28); second, by fatty change referred to degenerative changes set up by poisons reaching the liver; third, by amyloid change in long standing advanced cases with continued suppuration, not due to tuberculous toxin but probably from toxins of secondarily infected vomicae with pyogenic cocci. Mouisset and Bonnamour (29) believe that cirrhosis in tuberculous patients is nearly always due to concomitant alcoholism. White (30) further adds, "a cirrhosis due to actual tubercular disease has been described but does not exist."

The incidence of cirrhosis and tuberculosis of the liver, according to Kaufmann (19), is by no means frequent. In my opinion, this is true. In 2,701 autopsies at The University Hospital there were 43 cases of tuberculosis of the liver (solitary tubercles, miliary tuberculosis and disseminated tuberculosis of various types) with not a single instance of cirrhosis of the liver as an accompanying condition. Kaufmann further thinks it possible that tuberculous lesions in other parts of the body may, by the production of poisons, induce cirrhosis of the liver

without any tuberculosis of that organ. The association of hepatic cirrhosis and tuberculosis elsewhere in the body is more frequently seen. In the same number of autopsies (2,701), cirrhoses of the liver were recorded in 46 instances. This group included portal cirrhosis, Laennec's cirrhosis and the several forms of biliary cirrhoses, hypertrophic and atrophic cirrhoses. Extrahepatic tuberculosis was found associated with cirrhosis of the liver in 5 instances: fibrocaseous tuberculosis of the right upper lobe of the lung with disseminated tuberculosis, healed tuberculosis of right upper, calcified nodes in the mesentery of the small bowel, calcified nodule in the right lower lobe of the lung and questionable tuberculosis of the mediastinal nodes. Of these, 2 showed apparent activity, one was minimal and one showed activity with dissemination.

From the foregoing opinions one must conclude that the occurrence of cirrhosis of the liver from either intra- or extrahepatic tuberculosis is an unsettled problem with adherents on either side of the question. It is, therefore, not a frequent cause of icterus.

In the diagnosis of any of the foregoing types of tuberculosis as a cause of jaundice the presenting clinical picture of the patient must be the important factor. History may be of value. The degree of jaundice is about that observed in septic cases. The skin and sclerae are yellow and the urine may show the presence of bile. Van den Bergh test and icterus index as well as liver function tests may be helpful. In any patient who presents the typhoidal picture with jaundice and leucocytosis and on whom a definite diagnosis cannot be made, tuberculosis must always be considered as an aetiological factor. In addition to the tuberculin test, other diagnostic aids are the injection of 5 cc. of citrated blood into a guinea pig as reported by Rosenberger (31), the culture of blood collected in distilled water as performed by Clough (32) and the culture and demonstration of tubercle bacilli in the bile as stated by Sasano and Medlar (33).

Treatment is symptomatic except for primary tuberculosis of the gallbladder where surgery for its removal should be employed.

CASE REPORT

The patient, a fifty-six year old white woman, was seen in consultation with Dr. Daniel S. Shanahan, at Bon Secours Hospital, on December 22, 1938. She had been ill for three weeks. The illness was initiated on December 1, 1938 with a running nose and cough, which she treated herself until December 21, when, because of increased cough, shortness of breath and general fatigue, she called a physician. During this three-week period she had irregular chills, fever and fever blisters on her lips. Family history was irrelevant. She had influenza two years ago. She was accustomed to take one or two glasses of wine daily. A review of the systems was negative.

Physical examination disclosed an obese female, acutely ill with cyanosis of lips and fingers. Breathing was labored and cough frequent. Skin and scleral jaundice were not observed until December 30. Tonsils were scarred and injected. There was lag on the right side, dulness throughout the right chest with slight impairment on the left side below the angle of the scapula. Trachea and heart were displaced to the left and inspiratory stridor (bronchial) was heard over the right front and back with distant breath sounds. Blood pressure was 110/60. The abdomen was normal except for tenderness

in right upper quadrant. The clinical impression was pleural effusion, right, probably tuberculous.

Extensive laboratory studies were made and the pertinent findings are as follows: the urine showed a faint trace of albumen and a trace to one-plus bile. Leucocytosis was persistent and ranged from 11,000 to 18,350 with a polymorphonuclear predominance of 84 per cent to 91 per cent. Van den Bergh test showed a direct reaction with 1 mg. of bilirubin per 100 cc. of blood and an icterus index of 12. The bromsulphthalein test showed 25 per cent retention of dye in the serum after one-half hour. Tuberculin test, intracutaneous (1 to 100,000), was positive in twenty-four hours with erythema and induration. Pleural fluid was straw colored with a specific gravity of 1.017, a cell count of 650 with 98 per cent lymphocytes. Sedimentation rate (Cutler) ranged from 16 mm. to 18 mm. in one hour. The typhoid-paratyphoid agglutinations were consistently negative as were numerous blood cultures. X-ray films of the chest showed hydrothorax on the right with visceral displacement to the left. Gallbladder films (oral administration) showed poor concentration of dye.

The clinical course in the hospital was characterized by a continuously high temperature (101° to 104° F.) from the time of admission to death with the exception of an interval from January 11 to January 16, 1939 when it was normal. Pulse was consistently slow for this temperature, 80 to 100 per minute. Respirations ranged between 20 to 30 per minute. The clinical picture was that of the typhoid state with no complaints except pain when the abdomen was palpated. Repeated aspirations of the chest were performed and a straw colored fluid in amounts from 150 cc. to 1,000 cc. were removed. Drowsiness was progressive and the icteric tint of sclerae and skin became more pronounced before death. Cough was the most troublesome symptom for one week before death which occurred on February 6, 1939. Therapy consisted of a dietary regimen supplemented by thiamin chloride and glucose given intravenously. Codeine was used for cough.

An autopsy was performed by Dr. C. Bernard Brack:

The body was that of a well developed, somewhat obese white woman of about fifty years of age. External examination was negative except for *livor mortis* of the back and posterior surface of the arms and legs. The right lung was adherent to the parietal pleura over the whole lower lobe. The pleura was thickened and there was a thick layer of yellow exudate between the two surfaces. Scattered through this exudate were white tubercles measuring 1 to 2 mm. in diameter. There was a small amount of fluid in the pericardial sac.

The peritoneum contained 300 cc. of blood-tinged fluid. The whole parietal peritoneum and the visceral peritoneum were studded with white tubercles measuring 1 to 3 mm. These were slightly elevated and showed little variation in size.

The liver was not enlarged but the surface was studded with small white tubercles and on section the tissue was light brown in color with indistinct lobulations.

The spleen was slightly enlarged with a few tubercles on the surface. On section scattered small yellow tubercles were seen.

The kidneys appeared normal externally but in the cortex of one was a white nodule measuring about 5 mm.

There were a few fresh adhesions over the serosa of the intestine and the entire serosa was brittle with small white tubercles. Several larger patches were seen on the surface of the sigmoid colon where it forms a part of the cul-de-sac. The entire bowel was opened and the mucosa appeared normal throughout.

Microscopical examination: Lungs showed considerable emphysema and much carbon

pigment and several small patches of pyogenic lobular pneumonia. The section from the right base showed thickening and scarring of the pleura with a thick layer of fibrinous exudate on the surface. The pleura was heavily infiltrated with round cells and one or two hard tubercles and numerous multinuclear giant cells. There were a few caseous areas.

Liver showed large collections of fat in the liver cells and in some areas the cytoplasm was coagulated and dark red in appearance. There was moderate scarring in the periportal areas and scattered collections of round cells but no tubercles. The parenchymal cells displayed varying degrees of necrobiosis.

The spleen contained a few scattered small soft tubercles with caseous centres.

Throughout the kidneys there were scattered convoluted tubules where the epithelium stained deeply and contained colloid droplets.

Sections from the serosa of the intestine, parietal peritoneum, cul-de-sac of Douglas and omentum showed fibrinous exudate with scarring and chronic inflammation. In addition there were a number of giant cells with soft and hard tubercles.

Pathological diagnosis: Fibrinous pleurisy, tuberculous, right; disseminated tubercles in spleen; acute tuberculous peritonitis; early portal cirrhosis of the liver; lobular pneumonia; cloudy swelling of renal tubular epithelium.

SUMMARY

A discussion is herein given on the infrequency of tuberculosis as a cause of jaundice. Various disease entities are enumerated in which icterus might occur in tuberculosis. A case history is presented in which the clinical picture was that of the typhoidal type of acute miliary tuberculosis but the liver showed lesions as described by various authors as found in early tuberculous cirrhosis of the liver.

SUMARIO

Discútese en este trabajo la rareza de la tuberculosis como causa de ictericia, y enuméranse varias entidades patológicas en las cuales podría sobrevenir la última en coexistencia con la tuberculosis. Preséntase una observación en la cual el cuadro clínico era de granulia aguda de tipo tifoideo, y en que el hígado revelaba las lesiones descritas por varios autores como correspondientes a la cirrosis tuberculosa incipiente de dicho órgano.

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ELECTROCARDIOGRAPHY IN TUBERCULOUS PATIENTS[1]

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The results of electrocardiography on tuberculous patients are being studied in order to determine how much the information about the circulation, as conveyed by this method, might contribute to diagnosis, prognosis and therapeutic considerations in tuberculosis.

LITERATURE

Previous observations on the subject have been made by Simon and Baum (11) who found the average value of the T-wave in tuberculous patients lower than normal, indicating a weakened cardiac musculature. Hansen and King (7) report low voltage in one or more leads. D'Ambrosio (3) noted predominance of the right ventricle and alterations referable to toxaemia, but stated that changes in electrocardiograms on tuberculous patients are rare. White (12) describes how certain pulmonary lesions may produce partial obstruction of the pulmonary circulation, cor pulmonale, and right axis deviation. Master (9) and Anderson (2) observed right-axis deviation in pneumothorax, particularly that of the right lung, caused, in their opinion, by rotation of the heart rather than myocardial changes. Master noted that spontaneous pneumothorax produced axis deviation more frequently than artificial pneumothorax but, according to Anderson, degree or duration of the collapse had no influence on the resulting deviation. Grant (6) observed axis deviation to the right in all cases of pneumothorax whereas Simon and Baum find that collapse treatment does not always influence the electrocardiogram and may cause axis deviation to the left as well as to the right. Hansen and King (7) also state that in collapse therapy there may occur certain changes of amplitude which are not indicative of myocardial damage, and the type and degree of which are not predictable.

The electrocardiographic changes in pulmonary tuberculosis which have been noted by previous investigators and are discussed in this paper, may be grouped in four categories: (I) Changes due to disease of the heart associated with, but not caused by, tuberculosis. (II) Changes due to the influence of toxic substances upon the heart. (III) Changes due to impaired pulmonary circulation. (IV) Changes due to disturbances of position or innervation of the heart, not influencing the heart muscle itself.

MATERIAL

The observations in this article are based on 208 electrocardiograms of 151 patients, 148 of whom had some form of pulmonary tuberculosis, active, quiescent or arrested. One hundred and thirteen of these represent a series of consecutive cases who exhibited signs and symptoms that could have been due to heart disease and thus prompted a thorough investigation of the circulatory system. Thirty-six patients had no cardiac symptoms, but were subjected to cardiography and other diagnostic procedures in order to study possible alterations in their tracings. Of all 148, 27 were receiving unilateral, 10 bilateral artificial pneumothorax and 11 had thoracoplasties. In many of these cases

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repeated tracings, before as well as during collapse, have been obtained. The remaining 3 cases had idiopathic pneumothorax, and tracings were obtained during collapse and after reëxpansion of the involved lung.

I. Into the first of the previously mentioned categories which represents heart lesions complicating tuberculosis, but not apparently caused by the disease, fall the tracings of 40 patients. The following abnormalities were found:

Sinus arrhythmia (nonrespiratory) once (figure 1*a*); sinus bradycardia, twice; auricular extrasystoles, three times; A-V extrasystoles, twice. Four patients had auricular tachycardia (rates 210, 210, 144 and 130 respectively at normal temperature), one auricular flutter, one auricular fibrillation, 2 prolonged conduction time.

The tracings of one patient revealed widened and notched QRS-complexes of great amplitude, upward in lead-1, diphasic in lead-2, and downward in lead-3, with oppositely directed T-waves, the typical signs of left bundle branch block. (figure 1*a*).

In another case the electrocardiogram was quite similar, but the T-wave in lead-3 was isoelectric.

One patient showed small, widened, notched and diphasic QRS-complexes, the direction of the T-waves being opposite to that of the greater QRS-deflection, evidently intraventricular block.

Nine had ventricular extrasystoles.

Electrocardiograms with changes as are usually associated with myocardial infarction, were found in 5 patients. One of these, a man of fifty-nine, gradually developed severe substernal pain, gangrene of both legs and heart failure and eventually died. Electrocardiograms showed prominent Q-waves, and elevated take-off and sharp ascent of the ST-segment in leads 2 and 3; absence of the Q-wave, low take-off of the ST-segment and a diphasic T in lead-4; and frequent ventricular extrasystoles (figure 1*b*). At autopsy the findings were pulmonary tuberculosis, thrombosis of the left and sclerosis of the right coronary arteries, infarction of the anterior surface of the left ventricle at its apex and portions of the intraventricular septum, a mural thrombus of the left ventricle, a ball-valve thrombus at the bifurcation of the common iliac artery and passive congestion of various organs.

The second patient, a man of sixty-two, had collapsed on the street and been taken to a hospital where the diagnosis of bilateral active tuberculosis was made. After transfer to the Sanatorium electrocardiograms showed inversion of the T-wave in lead-1, and absence of the R-wave and a deeply-inverted T-wave in lead-4.

The tracings on a third patient, a man of forty-six who, during treatment for tuberculosis, complained of pain in the left chest and weakness in his left arm, revealed isoelectric T-waves in lead-1 and inverted T-waves in lead-4.

The fourth patient, a man of forty-six, who had been treated for coronary heart disease shortly before the onset of his lung disease, gave tracings with prominent Q-waves and elevated ST-segments followed by inverted T-waves in leads 2 and 3 (figure 1*c*).

Electrocardiograms on the fifth patient, a woman of sixty-six, who was suspected of having myocardial infarction, revealed inverted T-waves in leads 1 and 4.

In the tracings of 13 patients there was unspecified but unmistakable evidence of myocardial damage as indicated by low voltage of the QRS-complexes or small, diphasic or absent T-waves in the three customary leads, or low W- or M-shaped QRS-complexes in at least two leads. Three of these 11 cases will be discussed later.

In one case of transposition of all viscera the electrocardiogram was consistent with dextrocardia.

The particular value of these tracings becomes evident with the realization that such cardiac symptoms and signs as may be present, are apt to be misinterpreted as pulmonary or pleuritic in origin. Hence, the added information frequently had a definite bearing upon prognostic and therapeutic considerations in the individual case.

II. Evidence of damage to the heart by toxaemia is rarely found in electrocardiograms of tuberculous patients. The majority of those with far advanced disease and definite systemic reactions, excepting terminal cases with marasmus, protein depletion and anasarca, yielded tracings without changes attributable to toxaemia.

Three patients already mentioned under category I, however, developed tracings of severe myocardial damage with changes of the QRS-complexes and T-waves as previously discussed, during the course of very acute, ultimately fatal, tuberculous pulmonary lesions (figures 2*a* and *b*). Thus, it is conceivable that myocardial disease may have been caused by the influence of toxic substances from tuberculous lesions upon the heart muscle. These 3 cases, therefore, may fall into this group rather than the group of heart lesions merely associated with tuberculosis.

Individual ventricular extrasystoles are not necessarily of clinical significance. They were found in 9 patients. Two further cases, however, with previously normal rhythm, presented premature ventricular beats with trigeminal rhythm (figure 2*c*).

In one case they appeared at the beginning of an acute tuberculous empyema, in the other during the course of an acute febrile exacerbation of a chronic pulmonary lesion. In both cases the regular rhythm returned when the acute phase of the primary illness had come under control.

Similarly, one patient had episodes of auricular tachycardia at the rate of 210 when he developed tuberculous empyema and tuberculosis of the chest wall some time after an unsuccessful thoracoplasty (figure 2*d*).

It would appear, then, that toxic substances from acute tuberculous lesions may act upon the heart muscle and cause a state of muscular hyperirritability.

FIG. 1*a*. M. P., female, sixty-nine. Arrested tuberculosis. Sinus arrhythmia. Left bundle branch block.

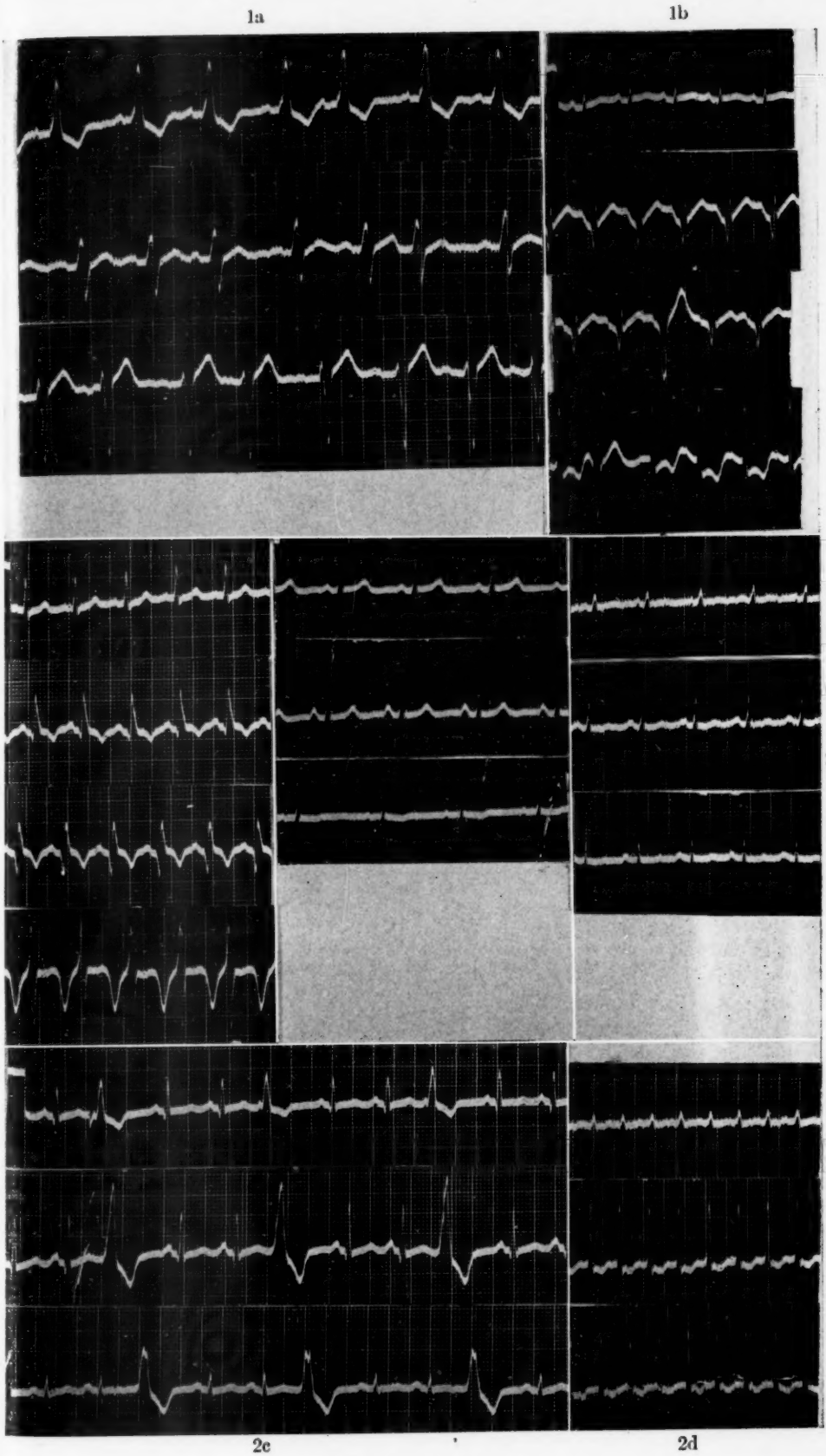
FIG. 1*b*. G. Y., male, fifty-nine. Pulmonary tuberculosis, quiescent. Developed chest pain due to repeated myocardial infarctions.

FIG. 1*c*. T. C., male, forty-six. Active pulmonary tuberculosis. Myocardial infarction, posterior surface.

FIGS. 2*a* and *b*. A. M., female, fifty-eight. Gradually developed myocardial degeneration during course of active pulmonary tuberculosis. The interval between the two tracings is one year. (*a*) Normal EKG. (*b*) The voltage has dropped about one-third and the T-waves are now barely discernible.

FIG. 2*c*. J. E., male, thirty-five. Developed premature ventricular beats with trigeminal rhythm at onset of tuberculous empyema, left.

FIG. 2*d*. J. H., male, forty-eight. One of a series of attacks of auricular tachycardia (rate 210) after unsuccessful thoracoplasty and development of tuberculous empyema and tuberculosis of the chest wall.



FIGS. 1, a–c; 2, a–d.

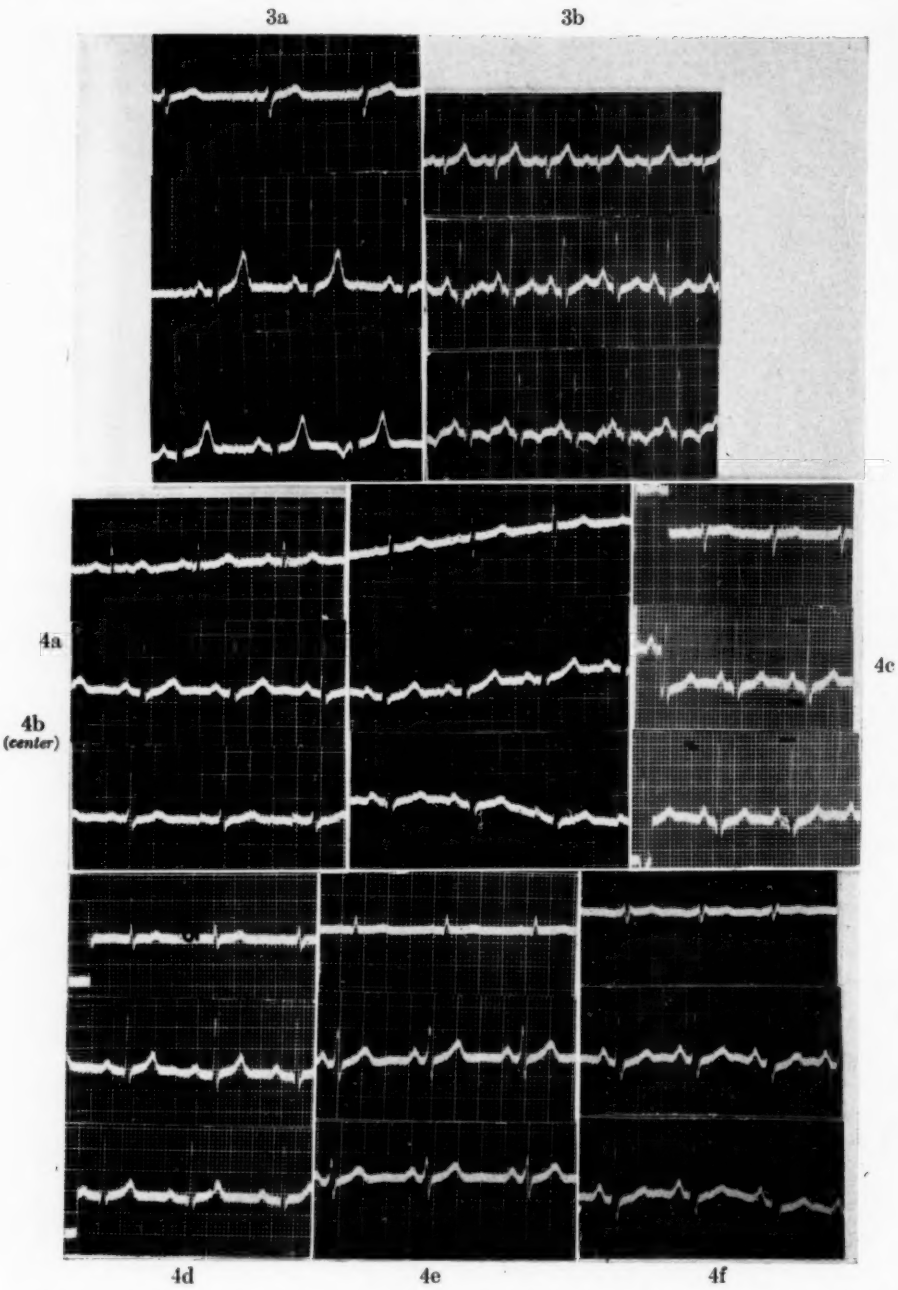


FIG. 3*a*. D. R., male, thirty-one. Arrested pulmonary tuberculosis. Symptom-free. EKG with rotation of the heart into vertical position. Mild right axis deviation.

FIG. 3*b*. G. J., female, thirty-one. Chronic fibrotic tuberculosis. More marked right axis deviation associated with right ventricular hypertrophy. Died two weeks after this tracing.

FIGS. 4*a* and *b*. A. G., female, twenty-six. Before and during artificial pneumothorax on the right. Slight rotation of the electrical axis to the right.

FIGS. 4*c* and *d*. J. H., male, twenty-one. After sudden complete idiopathic pneumothorax, right, and after reëxpansion. Mild right axis deviation during collapse. After reëxpansion return to normal axis.

FIGS. 4*e* and *f*. I. R., female, twenty-six. During artificial pneumothorax, right, and during bilateral artificial pneumothorax. Mild rotation of the electrical axis due to displacement of the heart. At least 50 per cent collapse on either side. No signs of circulatory disturbance.

III. It is known that the electrocardiogram may be influenced by abnormalities in the pulmonary circulation. Increased resistance to the action of the right heart may result in cor pulmonale, which in turn will frequently manifest itself in the electrocardiogram by right axis deviation. Moreover, McGinn and White (10) have pointed out that pulmonary embolism may result in acute cor pulmonale and may be accompanied by characteristic changes in the electrocardiogram, such as a prominent S-wave and low origin of the T-wave in lead-1, low origin and staircase ascent of the ST-segment in lead-2, presence of a Q-wave and inversion of the T-wave in lead-3 and an inverted T-wave in lead-4.

Since it is a known fact that a great number of vessels is destroyed within the reach of a tuberculous lesion it was of interest to determine whether the reduction of available pulmonary circulation could result in compensatory hypertrophy of the right heart and right axis deviation in the electrocardiogram. It would seem, however, that almost all of the tracings in cases of active pulmonary tuberculosis with wide-spread destruction of lung tissue showed no axis deviation. In a number of tracings in which the electrical axis was not normal, this was due to rotation of the heart around its anteroposterior axis resulting in vertical position rather than actual right-sided hypertrophy of the organ. Certain criteria will aid in differentiating the milder axis deviation produced by rotation from the marked axis deviation associated with ventricular hypertrophy. Rotation into the vertical position usually results in a small or even negative QRS, made up mainly of S in lead-1 and disproportionately high QRS-complexes, made up mainly of R in leads-2 and 3. The T-waves remain upright or tend to follow the direction of QRS (figure 3*a*). In actual right preponderance QRS of lead-2 is almost invariably diphasic and the direction of the T-waves in leads-1 and 3 tends to be opposite to that of the greater QRS-deflection (figure 3*b*). The same reasoning, of course, is also valid for horizontal position of the heart and left-sided preponderance if the above criteria are exchanged for leads-1 and 3, respectively.

Thus interpreted, there remain only the tracings of 5 patients indicating right-axis deviation due to actual hypertrophy of the right ventricle. Their main symptoms were dyspnoea, orthopnoea, cyanosis and early oedema. They had a very chronic type of tuberculosis and their roentgenograms showed marked fibrosis rather than wide-spread infiltrative lesions. (In one case it was impossible to definitely establish tuberculosis as the cause of fibrosis.) Their dyspnoea seemed to be out of proportion to the amount of tuberculosis demonstrable in the lungs. All 5 died, in a manner suggesting cardiac failure, within an average of sixty days after discovery of right-axis deviation in the electrocardiogram.

In two of these cases, autopsies were performed: In one, S. M., male, twenty-eight, the findings were cardiac hypertrophy and dilatation, most marked in the region of the right auricle, chronic pulmonary tuberculosis with cavitation in the right upper and lower lobes, acinous and acinous-nodose lesions in all lobes, extensive pulmonary fibrosis and emphysema and congestion of the spleen and liver.

In the other, G. J., female, thirty-one, there was hypertrophy and dilatation of both ventricles, pulmonary tuberculosis with acinous-nodose lesions in all lobes, cavitation in the right upper and lower lobes and the left lower lobe, bilateral obliterating fibrous

pleuritis, considerable pulmonary fibrosis and emphysema and congestion of the spleen, liver and kidneys. In both cases it was evident that death was due to heart failure, secondary to extensive pulmonary fibrosis.

In a group of patients with most extensive infiltrative and excavating tuberculous lesions, no signs of cor pulmonale and right-axis deviation were encountered. Hence it would appear that the pulmonary vessels in the remaining unaffected portions of the lungs maintain an adequate circulation, no matter how great the destruction of parenchyma may be. In the presence of generalized fibrosis, however, the compensatory emphysema accompanied by a generalized capillary elongation, narrowing, and obliteration, on one hand, and the frequently encountered pulmonary arterial sclerosis on the other, must be held responsible for the development of cor pulmonale and right-axis deviation. The appearance of right-axis deviation in a patient with chronic pulmonary tuberculosis should thus be regarded as an ominous sign.

IV. The tracings with axis deviation due to displacement of the heart may resemble those of one-sided ventricular preponderance. Shifting of the heart to one side or the other does not alter the electrocardiogram in its customary three leads. Rotation around the anteroposterior axis into or beyond the vertical position ("drop-heart") or around the vertical axis toward the left, may produce right-axis deviation. Rotation around the anteroposterior axis toward the horizontal position (for example, in obesity) or around the vertical axis toward the right, may produce left-axis deviation. The criteria which help differentiating axis deviation due to displacement from that of actual one-sided cardiac hypertrophy have been mentioned previously (section III). The distinction is important as displacement of the heart would not commonly entail serious consequences, whereas a diagnosis of cardiac hypertrophy is of great clinical significance.

The question was investigated whether collapse treatment might interfere with the pulmonary circulation and produce electrocardiographic changes. Of 49 patients with normal hearts and pulmonary collapse, 26 with unilateral artificial negative-pressure pneumothorax, 10 with artificial bilateral pneumothorax, 10 with thoracoplasty and 3 with idiopathic pneumothorax, none showed axis deviation. Serial tracings were obtained on 12 patients with pneumothorax and 4 patients with thoracoplasty before and during the presence of collapse, and on 3 cases of idiopathic pneumothorax during collapse and after reëxpansion. The tracings of these 18 patients likewise did not reveal axis deviation so as to indicate cardiac hypertrophy, although a number of patients developed a prominent S-wave in lead-1 during the period of collapse, no matter which side was under collapse (figures 4*a*, *b*, *c*, *d*, *e* and *f*). These findings concur with the results of a clinical study by Hurst and Brand (8) who found a normal circulation time and no consistently elevated venous pressure in pulmonary collapse. Feinsilver (5) also obtained an unchanged venous pressure in cases of artificial pneumothorax and thoracoplasty, but found that the arm-to-lung

circulation time was shortened. His explanation is that although the blood flow through the pulmonary artery of the collapsed lung is reduced, this lung depending for its supply on the bronchial circulation, a proportionately larger volume of blood passes the pulmonary artery of the uncollapsed lung in the time unit, thus maintaining the pulmonary circulation on an adequate level. These observations, as well as the electrocardiographic findings, bear out the belief that collapse therapy does not give rise to significant strain upon the right heart, provided, of course, that abnormalities of the pulmonary circulation itself can be excluded. If the pulmonary artery and its ramifications are diseased, their adaptability impaired and their calibre fixed, right heart failure might conceivably supervene as a result of the pulmonary collapse.

Mention should be made of two cases of sinus arrhythmia, nonrespiratory in type, accompanied by episodes of bradycardia. One had pneumothorax on the right with apical adhesions, the other an arrested pulmonary lesion with a great deal of apical scarring. It is quite possible that the arrhythmic bradycardia in these 2 cases was caused by stimulation, due to traction and the presence of scar tissue, of vagus fibres beneath the mediastinal pleura. Carotid sinus, bulbus or abdominal pressure did not significantly reduce the normal heart rate between attacks.

SUMMARY

The literature on the subject is reviewed.

The material used in this article is described.

1. Electrocardiograms proved to be helpful in diagnosing heart lesions in tuberculous patients, especially when it was doubtful whether the symptoms were of cardiac or pulmonary and pleural origin.

2. Acute pulmonary tuberculosis appears to have been the cause of myocardial disease in only 3 cases. In 2 other cases premature ventricular beats with trigeminal rhythm developed, and paroxysmal auricular tachycardia in one, probably as a result of toxaemia.

3. The criteria for the differentiation in the electrocardiogram between right axis deviation due to displacement of the heart and ventricular hypertrophy are reviewed. In the great majority of cases with extensive acute and infiltrative pulmonary tuberculosis no right axis deviation was observed. In pulmonary fibrosis right axis deviation is more likely to develop and must be regarded as an ominous sign.

4. If the pulmonary vessels are normal, collapse therapy does not seem to seriously interfere with the pulmonary circulation. Displacement of the heart may occur, but right axis deviation due to right ventricular preponderance has not been observed. Two cases of sinus arrhythmia and periodical bradycardia are briefly discussed.

SUMARIO

En este trabajo repásase la literatura relativa al asunto, y se describe el material utilizado.

1. Los electrocardiogramas resultaron útiles para diagnosticar las lesiones cardíacas en los tuberculosos, en particular cuando había dudas sobre si los síntomas reconocían origen cardíaco o neumopleural.

2. Sólo en 3 casos pareció la tuberculosis pulmonar aguda ser la causa de la afección miocardíaca. En otros 2 casos se presentaron latidos ventriculares prematuros con ritmo trigémino, y en uno taquicardia auricular paroxística, probablemente debida a la toxemia.

3. Analízanse las pautas aplicadas para la diferenciación electrocardiográfica entre la desviación del eje derecho debida a desplazamiento cardíaco y la hipertrofia ventricular. En la gran mayoría de los casos en que había extensa tuberculosis pulmonar aguda con infiltración no se observó desviación del eje derecho, siendo más probable que se presente ésta en la fibrosis pulmonar, debiendo ser considerada entonces como signo de lo más grave.

4. Si los vasos pulmonares se encuentran en estado normal, la colapsoterapia no parece afectar mayor cosa la circulación pulmonar. Puede sobrevenir desplazamiento del corazón, pero no se ha observado desviación del eje derecho debida a predominio del ventrículo derecho. Repásanse sucintamente dos casos de arritmia sinusal y bradicardia periódica.

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THE POLYARCUATE DIAPHRAGM[1]

EPHRAIM KOROL[2] AND ALTON J. SAXTON[2]

Definition: A roentgenographic and roentgenoscopic appearance of the diaphragm in which the muscle, during its inspiratory contraction, presents two or more arches on each side of the heart, instead of the familiar single dome. Typically, the lungs are symmetrically and well aerated, the costophrenic angles are deep, and there are no signs of pulmonary contraction or of diaphragmatic adhesions.

The phenomenon is observed only in deep inspiration, and in the erect position, and for this reason is not seen postmortem. It can be simulated in the cadaver by manual stretching of the diaphragm, and in the experimental animal by provoking a deep inspiration (1).

Incidence: The condition is uncommon in the young and in the presence of inflammatory pleural and pulmonary changes. It would seem that good inflation of the lungs and freedom from pleural adhesions are necessary for the several muscle bundles of the diaphragm to find expression on the roentgenogram. It does not occur in children under the age of ten (2), but becomes frequent after middle age, being more common in males (3). It is seen in a majority of cases of chronic bronchitis and emphysema.

Among our middle-aged veterans the phenomenon is seen in 30 per cent of all cases reporting for roentgen examination of the heart or lungs. In 100 unselected cases of bronchial asthma, the polyarcuate diaphragm appeared in 54 cases.

Physiological considerations: The diaphragm, by active contraction in inspiration and by its muscle tone in expiration, plays a rôle in protecting the chest organs from atmospheric and abdominal pressures. The position and shape of the diaphragm vary physiologically with the changing pressure relations. In the erect position, the pressure in the upper abdomen being low due to the sagging abdominal viscera, the diaphragm descends and is flattened out. In the recumbent position the diaphragm rises into the chest and its dome is more convex. In the sthenic man with good tone in the abdominal muscles the diaphragm stands high in the chest, while in the visceroptotic individual with weak abdominal musculature the diaphragm is low and flat even in the absence of pulmonary emphysema.

At birth the diaphragm stands high in the chest, at the third rib, and throughout life it goes through a slow migration downward (4) so that in adult life the diaphragm stands two ribs lower than at birth. This descent of the diaphragm is in part due to the gradual loss of tone in the abdominal muscles which begins rather early in life. In the muscles of the neck and chest (the inspiratory muscles) the loss of tone sets in much later in life. In the early twenties the abdomen

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in most people begins to sag due to weakening of the abdominal (expiratory) musculature. The better preserved inspiratory muscles raise the ribs, while the diaphragm descends with the abdominal viscera. Simultaneously, atrophic emphysematous changes in the lungs also set in. The retractile properties of the lungs are reduced and the intrathoracic pressure rises toward the atmospheric, while the pressure in the upper abdomen tends to sink. Thus, both the ribs and the diaphragm assume a more inspiratory position, the residual air accumulates in the lungs and the vital capacity decreases.

Embryologically the anterior bundles of the diaphragm originate from the same segments as the rectus abdominis (5) and like the abdominal muscles it seems to undergo atrophic changes early, while the lumbar bundles of the diaphragm still retain vigorous tone. Histological studies of the muscle in aged individuals and in cases of pulmonary emphysema have shown this association of atrophy of certain muscle bundles with well preserved or hypertrophied bundles in other parts of the diaphragm (6, 7) in the same person.

It has been frequently observed clinically that, in cases of emphysema and bronchial asthma, portions of the diaphragm, usually the sterno-costal bundles, are weak and inert and offer no resistance to the respiratory pressure changes between the abdomen and chest (8). In inspiration this part of the diaphragm may paradoxically move upward, passively following the movement of the ribs and the rise of intraäbdominal pressure caused by the descent of the better preserved bundles of the diaphragm. In the asthenic visceroptotic individual the paradoxical behavior of the diaphragm can occur in the absence of pulmonary emphysema (9, 10). In these cases the anterior portion of the diaphragm is flat and overinflated lung tissue can be seen on the roentgenogram between the heart and the diaphragm. In the erect position, and particularly if emphysema is present, this part of the diaphragm is sometimes actually inverted into the abdomen.

In the sthenic person with high abdominal pressure the weak anterior part of the diaphragm may bulge upward above the dome formed by the normally contracting bundles. This tumor-like projection of the diaphragm has been mistaken for tumor of the liver, ecchinococcus cyst (11), and diaphragmatic hernia (12).

Pulmonary emphysema is commonly most advanced in the upper (anterior) lobes, and this tends further to depress and inactivate the anterior portion of the diaphragm. However, this is not invariably the most displaced part of the diaphragm. Due to some vascular or bronchial accidents the lower lobes may be the seat of greatest overinflation; also, the abdominal pressure under certain conditions may be higher in the anterior than in the posterior regions of the abdomen.

ILLUSTRATIVE CASES

Case 1: World War veteran, aged forty-four, coal miner, was admitted to the hospital on June 3, 1937, with pain in left chest and fever which had developed the previous day. He had had a cough productive of yellow sputum for five years. The man was slender

and emaciated and had a barrel chest. There were physical signs of asthmatic bronchitis and of an area of consolidation in the left upper lobe.

The roentgenogram of June 4, 1937 (figure 1) shows a pneumonic infiltration on the left side above the fourth rib. The right lung shows emphysematous bullae in the apex and upper mediastinal region. The lung bases are very transparent and the costophrenic angles wide. The diaphragm presents four distinct folds on each side of the heart. Some of the folds are convex upward, others are flat and one, in the left axillary region, is convex downward. There was continued fever and no crisis occurred. The cough and dyspnoea increased and the expectoration became foetid. The patient died on June 13, 1937.

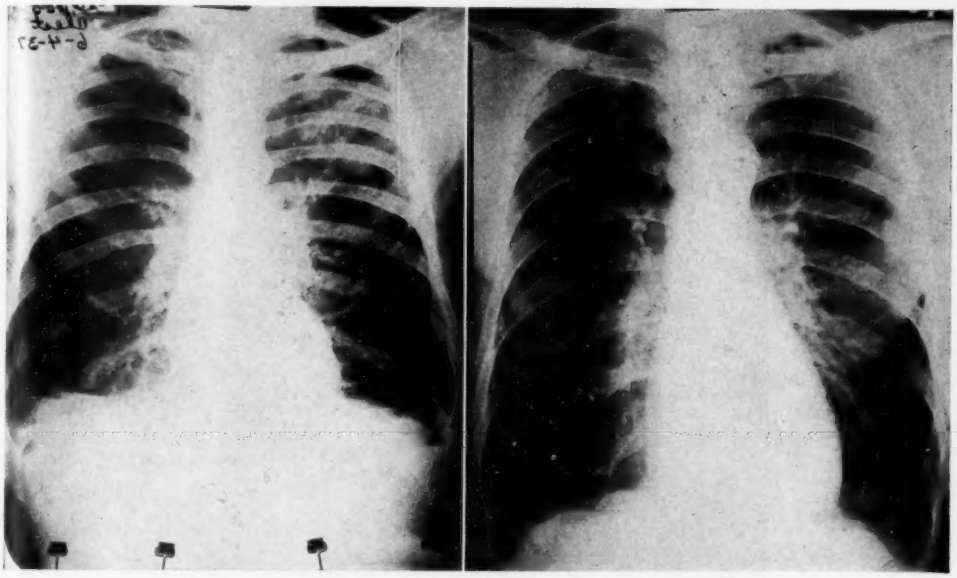

FIG. 1. (Left). The diaphragm shows four folds on each side. On the left side the lowest fold is convex downward. Marked pulmonary emphysema. In the right apex and superior mediastinum thickened walls of emphysematous bullae show plainly. Pneumonia in left upper lobe. Postmortem showed no pleural adhesions.

FIG. 2. (Right). Three folds on each side, the lowest one is convex downward. Marked emphysema in the lung bases. Note the emphysematous lung between the heart and diaphgram.

The film of June 10, 1937 shows the left lung contracted while the area of consolidation has increased to involve the bulk of the lung. The diaphragm is elevated on the left side, its contour is smooth, the folds having disappeared on this side. The right lung remains clear and hyperaerated and the four diaphragmatic arches persist on this side.

Postmortem examination showed gangrene of the left upper lobe with extensive fibrinous pleurisy and anthracosis in the lower lobe. The right lung was emphysematous and filled the entire pleural cavity. It showed much anthracosis. There were no pleural adhesions on the right side. The liver surfaces were smooth.

Comment: A coal miner with emphysema and chronic bronchitis presented the typical polyarcuate diaphragm bilaterally. The arches were rather shallow

and one of them was inverted, due to a combination of emphysema and visceroptosis. The irregularities of the left hemidiaphragm disappeared with the development of pneumonia on this side. Postmortem examination showed that the polyarcuate diaphragm was not caused by pleural adhesions nor by ridges in the liver.

Case 2: The veteran, a carpenter by occupation, was first examined on August 2, 1921. He complained of occasional attacks of asthma. He was slender and poorly nourished, but showed no abnormal physical signs in the lungs.

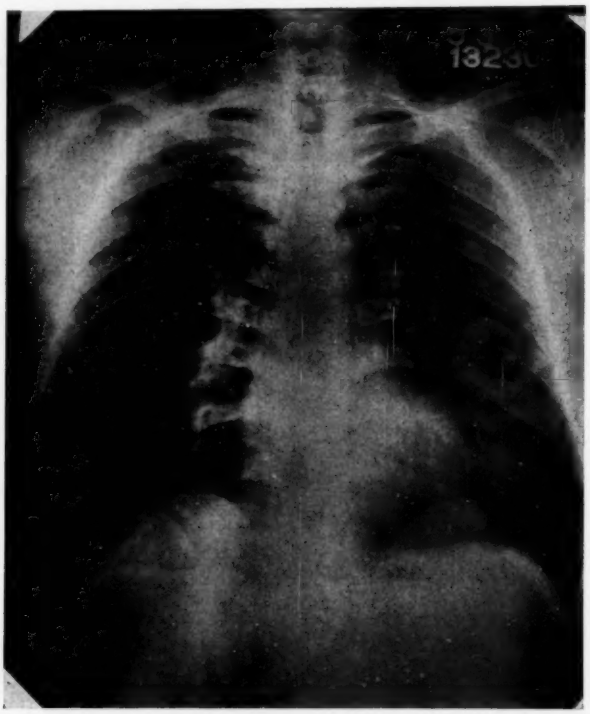

FIG. 3. Three arches on the right side, two on the left. Emphysema of lung bases.

On December 12, 1929 a roentgenographic examination disclosed the diaphragm irregular in contour. On April 3, 1931, fluoroscopic examination showed good excursion of the diaphragm, with no disturbances of contour.

On June 25, 1934, the veteran complained of frequent attacks of asthma. He was 68¼ inches tall and weighed 115 pounds. The chest was very thin, the abdomen showed visceroptosis. The signs in the lungs were those of asthmatic bronchitis. The roentgen films, dated June 30, 1934, show very transparent lungs with some flattening of the diaphragm, but no diaphragmatic folds. The films of September 16, 1936, show very large lungs, the ribs horizontal, the heart lifted from the diaphragm by emphysematous lung. The latter shows two arches on each side of the heart shadow. The lateral film made at this time shows that the higher arch on each side represents the anterior sternocostal bundles of the diaphragm. The man was forty-four years old.

On May 5, 1939, the man complained of continuous asthma with exacerbations during the ragweed season. The lungs were hyperresonant, the breath sounds feeble and musical râles were diffuse throughout both lungs. The roentgen films (figure 2) show hyperaeration of the lungs, particularly at the bases. The heart is separated from the diaphragm and the costophrenic sulcus is large on each side. The stereoscopic examination shows the uppermost fold to be anterior in location, the lowermost fold, concave downward, to be posterior. The last examination, dated December 31, 1940, disclosed an increase in the dyspnoea, no change in the objective physical or X-ray findings.

A comparative study of the several roentgenograms made during the past seven years, show a gradual enlargement of the heart and increase in size and density of the large pulmonary arteries, in addition to the changes in the contour of the diaphragm.

Comment: A visceroptotic individual afflicted with bronchial asthma has been under observation for twenty years. Disturbed action of the diaphragm was first noticed at the age of thirty-seven. The diaphragmatic folds gradually increased in number and depth and the posterior fold is convex downward. During the period of observation the heart enlarged and the pulmonary arteries have undergone arteriosclerotic changes.

Case 3: The veteran had been wounded and gassed during the World War. On October 29, 1919, an examination of the chest disclosed no abnormal physical signs.

On September 9, 1920, he complained of shortness of breath and a productive cough. There were musical râles in the lungs.

On October 13, 1936, he was taking adrenalin periodically for the relief of asthma. Age forty, height 64 inches, weight 168 pounds. His chest was broad and his abdomen prominent. There were physical signs of asthmatic bronchitis. The skin was sensitive to ragweed pollen. The stereo-roentgenograms show a well aerated chest of a hypersthenic individual with deep costophrenic angles. The diaphragm shows three arches on the right and two on the left side. The topmost arch is anterior in position on the right, but posterior on the left side.

The man continued to gain weight while his dyspnoea increased. On May 3, 1939, the films (figure 3) showed more emphysema and the diaphragmatic folds were more prominent. The heart was larger than on the film of October 13, 1936.

Comment: An asthmatic of sthenic build has been under observation since the first World War. Diaphragmatic folds were first noticed at the age of forty. Due to adiposity, the arches were all convex upward. They became more prominent as the emphysema progressed.

DISCUSSION

The statement has been made repeatedly (13, 2) that the diaphragmatic folds are caused by the ridges of the liver which are often seen postmortem in old people. Our observations do not bear out this opinion. We do not know of a single case where the polyarcuate diaphragm was shown to be associated with ridges or furrows in the liver. In 2 cases that we followed to autopsy the liver was free of ridges. In one case with pronounced folds of the right hemidiaphragm a pneumoperitoneum was produced and the liver was separated from the diaphragm by a collection of air. The roentgenogram shows the liver surface

smooth and the folds in the diaphragm unaltered. The persistence of the diaphragmatic irregularities after the induction of pneumoperitoneum can be seen in the works on pneumoperitoneum (14).

The liver furrows are much more common in females and they have a vertical direction (15). The diaphragmatic folds are more common in the male sex and have a horizontal arrangement.

It is recognized that certain diseases of the liver, such as abscess, tumors, cysts of the liver, associated with enlargement of the organ, can produce displacement and disfigurement of the diaphragm. However, these conditions are usually unilateral, are associated not with overinflation but rather with compression of the lung, and the resultant deformity of the diaphragm is permanent, persisting in both phases of respiration and in all positions.

Pronounced bilateral folds are usually associated with pulmonary emphysema and clinical signs of asthmatic bronchitis. More moderate deformities of the diaphragm, particularly if limited to the right side, are often seen without signs of bronchitis and emphysema. Any condition in the chest or abdomen which tends to produce an inspiratory position of the ribs and diaphragm is likely to show this asynchronous and unequal contraction of the components of the diaphragm.

The phenomenon is thus often seen in visceroptosis (16) and emaciation due to depression of the diaphragm, in obesity and kyphosis due to elevation of the lower ribs, also in artificial pneumothorax with depression of the diaphragm (17).

SUMMARY

1. The polyarcuate diaphragm occurs independently of pleural adhesions and of the physiological liver furrows.

2. The condition occurs in middle-aged people with weakened abdominal wall and atrophic changes in the diaphragm and emphysematous changes in the lungs. It is caused by asynchronous and unequal inspiratory contraction of the several muscle bundles of the flattened diaphragm.

3. The well marked diaphragmatic folds are usually seen in cases with advanced emphysema and bronchitis. Less pronounced folds in the diaphragm can be seen without frank emphysema in various conditions of the chest and abdomen which cause an exaggerated inspiratory position of the ribs or diaphragm.

SUMARIO

1. El diafragma poliarqueado se presenta independientemente de la existencia de adherencias pleurales y de surcos hepáticos fisiológicos.

2. El estado preséntase en personas de edad media que tienen la pared abdominal debilitada y alteraciones atróficas en el diafragma y enfisematosas en los pulmones, debiéndose a la contracción asincrónica y desigual a la inspiración de los varios fascículos musculares del diafragma aplastado.

3. En los casos avanzados de enfisema y bronquitis suelen observarse repliegues diafragmáticos bien definidos. Pueden observarse repliegues menos pronunciados en el diafragma sin enfisema declarado en varios estados del

tórax y abdomen, que exageran la posición de las costillas o el diafragma a la inspiración.

We wish to express our appreciation to the Medical Director and the Research Subdivision of the Veterans Administration for the collection of material and for encouragement given in this work.

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APPETITE IN CHILDREN WITH EXTRAPULMONARY TUBERCULOSIS[1]

JOSEPH D. WASSERSUG

Anorexia is a frequent finding in patients suffering from active tuberculosis. Although the exact cause of this symptom is not well understood, a variety of methods and drugs have been used empirically in an attempt to stimulate appetite. This paper represents a study of more than two years in which vitamin B and insulin were both used in children suffering from active extrapulmonary tuberculosis.

LITERATURE

In pulmonary tuberculosis many patients show a deficiency of vitamin A (10) and vitamin C (14, 20). It is a fact that the average American diet is unsatisfactory with respect to vitamin B_1 (7, 13) and even hospital diets have been criticized for the same reason (17). Besides, in disease, especially in prolonged fevers, the need for vitamin B is increased beyond normal (1, 6, 13, 17, 23). It was felt therefore that perhaps some of our patients had a vitamin-B deficiency which was not adequately treated by the routine sanatorium diet and that, if the diet were supplemented by vitamin B, the appetite in these patients would improve.

Research on the effect of vitamin B upon appetite has proceeded from several directions. In animals and humans where a vitamin-B dietary deficiency has been experimentally produced, anorexia was a common and early symptom and it was relieved by adequate dietary measures (3, 4, 9, 12, 21). In cases of "functional" chronic gastrointestinal disease, vitamin B added to the diet improves appetite almost invariably (11, 14, 18). Cowgill (5) states that "anorexia should be of significance to the clinician especially because it may occur in the absence of any other signs that the vitamin-B supply is inadequate." "In every case of appetite failure," says Peters (16) "the vitamin-B content of the diet should be considered."

Various attempts have been made to stimulate appetite in children by relatively large doses of vitamin B and good results have been obtained in the absence of definite active organic disease (8, 19, 23). Aring (1) says that in fever the maintenance dose should be 5 to 10 mg. of thiamine chloride daily and recommends the use of 50 mg. of thiamine intravenously for one week as a therapeutic test. Cowgill (7) states that preschool children need 25 I.U. thiamine per 100 calories daily. The adult requirement is 300–350 I.U. and this is equivalent to about 1 mg. of pure thiamine. Traut (21) suggested the use of 30 mg. of thiamine subcutaneously for ten days as a therapeutic test. This dose was adopted and used in some of the work described in this paper. Recently Nichols and Compere (15) used insulin as an aid to appetite in children with bone and joint tuberculosis and obtained good results.

CLINICAL DATA

Cases selected: A group of 12 male children whose ages varied from five to eleven years was selected. Eleven of these patients had active spine or hip

[1] From Lakeville State Sanatorium, Massachusetts Department of Public Health, Middleboro, Massachusetts.

tuberculosis and the twelfth had active tuberculous cervical adenitis. In every one of these patients appetite was poor for relatively long periods of time. Of these patients, 3 were used as controls, 4 patients were given only yeast (equivalent to 120 I.U. of thiamine) daily for four months, 2 patients were given

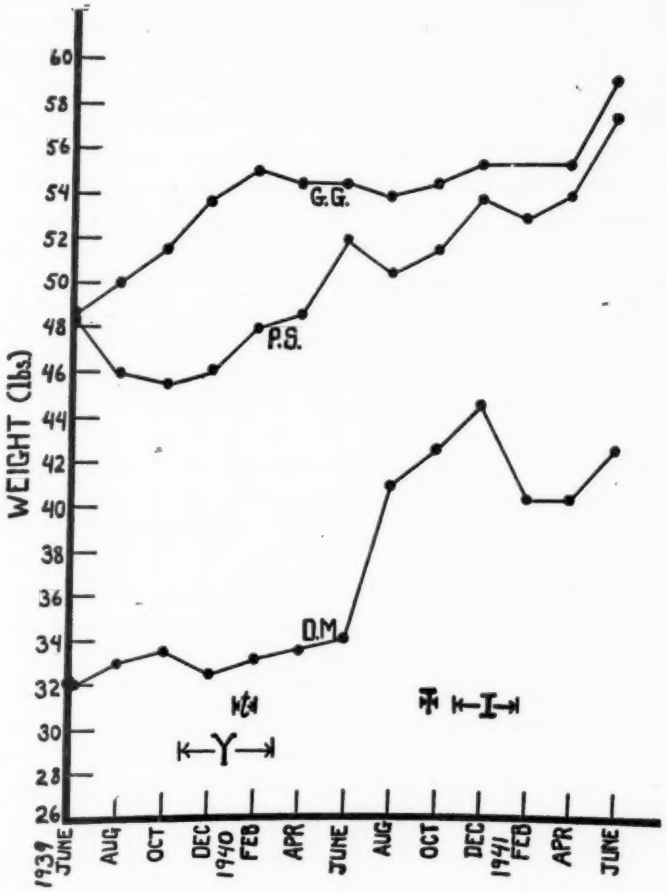

CHART 1. Weights (lbs.) of children receiving yeast, thiamine and insulin. t = Thiamine chloride 5 mg. daily by mouth for thirteen days; T = Thiamine chloride 30 mg. daily subcutaneously for ten days; Y = Yeast 120 I. U. daily for four months; I = Insulin, 3 to 5 units three times daily before meals for three months.

insulin alone for three months and the remaining 3 patients were given yeast, thiamine and insulin at different intervals (chart 1).

Diets: The thiamine chloride content of our diets was calculated from tables furnished by the United States Department of Agriculture (2). It was found that a typical menu offered to our children contained C319 P78 F102 Cals2506 and thiamine 437 I.U. On the other hand, the amount of food actually eaten by 4 children in our series over a period of three days was found to average daily

C110 P46 F52 Cals1060 and thiamine 183 I.U. It is obvious that whereas the theoretical intake of thiamine is adequate, the actual intake of these patients is low.

RESULTS

1. *Patients receiving yeast only:* Four children were given yeast containing 120 I.U. of thiamine chloride daily in divided doses. If this amount of vitamin B_1 is added to the average actual intake of 183 I.U., the total daily intake was approximately 300 IU. This means that for four months these patients received about 30 I.U. per 100 calories or what amounts to a theoretical adequate intake. Yet no noteworthy increase in appetite was noted. The average gain in weight of these children in six months prior to treatment was 2.0 lbs. During the four months of treatment, the average gain in weight was 2.1 lbs. In the six months after treatment was concluded, the gain was only 1.7 lbs.

2. *Patients receiving insulin only:* Two patients were given 3 to 5 units of regular insulin three times daily before meals for a period of three months. For three months before the administration of insulin these patients each gained 2 lbs. During the experimental period they gained another 2 lbs. In the next three months they averaged 2.5 lbs. In neither patient did appetite improve remarkably.

3. *Patients receiving yeast, thiamine and insulin:* Another 3 patients whose appetites did not improve on yeast alone were given in addition 5 mg. thiamine chloride daily by mouth for thirteen days. This supplemented their diet by 1,665 I.U. of vitamin B_1 daily. Since appetite did not improve even with this apparently adequate intake, it was felt that perhaps the vitamin was poorly absorbed and six months later thiamine chloride was given subcutaneously in doses of 30 mg. daily for a period of ten days. It was felt that if anorexia was due solely to vitamin B_1-deficiency, this would be corrected by such a large dose of thiamine chloride. However, no change was noted in appetite. After a month's pause, these patients were then given 3 to 5 units of insulin before each meal for a period of three months. No improvement in weight or appetite was observed during this period. (See chart 1.)

CONCLUSIONS

It is difficult to draw definite conclusions from this group of 12 children but the results indicate that in the presence of an active tuberculous lesion neither vitamin B_1 nor insulin exerts an appreciable effect in stimulating appetite. Conversely, experience has shown that when the lesion becomes quiescent (as determined clinically and roentgenologically) appetite spontaneously improves. Further work is advisable however to determine whether the vitamin-B complex (instead of thiamine chloride) in massive doses would have a stimulating effect on the appetite of patients suffering from active extrapulmonary tuberculosis.

CONCLUSIONES

Resulta difícil sacar conclusiones bien definidas de este pequeño grupo de 12 niños, pero el resultado indica que cuando existe una lexión tuberculosa activa

ni la vitamina B_1 ni la insulina ejercen efecto apreciable en lo tocante a excitar el apetito. Por el contrario, la experiencia ha demostrado que cuando la lesión se vuelve quiescente (clínica y roentgenológicamente), el apetito aumenta espontáneamente. Conviene realizar más estudios para determinar si el complejo vitamínico B (en vez del cloruro de tiamina) a dosis masivas, ejercería un efecto estimulante sobre el apetito de los enfermos que padecen de tuberculosis extrapulmonar activa.

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CONTROLLED STAINING OF MYCOBACTERIUM TUBERCULOSIS[1]

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The literature of thirty or forty years ago occasionally refers to the view that in staining suspected materials for *Mycobacterium tuberculosis* many organisms are not stained by the usual procedure. This opinion was strengthened by the work of Spengler (1) and Much (2), who described special forms of the organism which are not readily recognized, if at all, by our usual staining method.

In practice it must be evident to all who have had considerable experience in staining that an occasional preparation is found in which the result is unsatisfactory, although treated according to standard procedure. If the bacillary population is sufficient, one can tell momentarily whether the organisms are stained satisfactorily, and restaining may be resorted to if desired. However, if the population is sparse, much time may be lost in determining the character of the staining and, if the preparation is reported negative, doubt exists as to whether it has been properly stained at all.

Of the last 6,000 preparations examined in our laboratory, 1,573 showed one or more organisms per field, 1,346 showed less than one per field and 3,081 were totally negative. Satisfactory stain penetration is necessary, then, in the second and third groups representing 4,427 or 73.8 per cent of these preparations, if maximum results are to be obtained.

The common causes of understaining are defective staining solutions, insufficient time allowed for staining, over-decolorizing and location of the organisms in the deeper layers of the film where the stain cannot penetrate readily. In order to overcome these difficulties and secure satisfactory stain penetration, for the past nine years we have placed a positive control at the corner of each slide to be stained simultaneously with the unknown. The character of the staining of the control enables us to accept or reject a stained film according to a definite standard. We designate this method as controlled staining. Our experiments and practical experience with the method are presented.

TECHNICAL PROCEDURE

Preparation of the control: A mucoid specimen of sputum is selected, containing from one to three organisms per field, or if less than this number, organisms from a purulent specimen are washed with saline, centrifugated and the liquid poured off. This is repeated about three times, to remove all enzyme from the specimen. The organisms taken up in a few drops of saline are then added drop by drop to the mucoid specimen as desired. After shaking with glass beads to secure uniform distribution the control is kept at 5°C. If all enzyme has been removed, the organisms will keep in good condition for a month or longer, but with the first evidence of peeling of the control in staining, fresh mucoid material may be added or a new control is made. A small glass rod inserted into the cork of the container serves to spread the material on the slide. Only a very small amount of the control is streaked on the slide, very thin at one end, overthick at the other

[1] From the Laboratory of the Pottenger Sanatorium, Monrovia, California.

so as to be plainly visible with picric acid as counterstain. To prevent scattering of the organisms to the unknown by the breaking of small air bubbles in drying, a sterile glass slide should be held as a screen while the control is drying. A simple method is to insert the end of the slide into a groove cut in the side of a cork, which holds the slide in vertical position (figure 1A).

Preparation of suspected material: The suspected material is diluted from three to ten times with saline and homogenized by mechanical shaker for ten minutes. A film is then made by transferring a portion to the slide which is tilted so that one end in drying is very

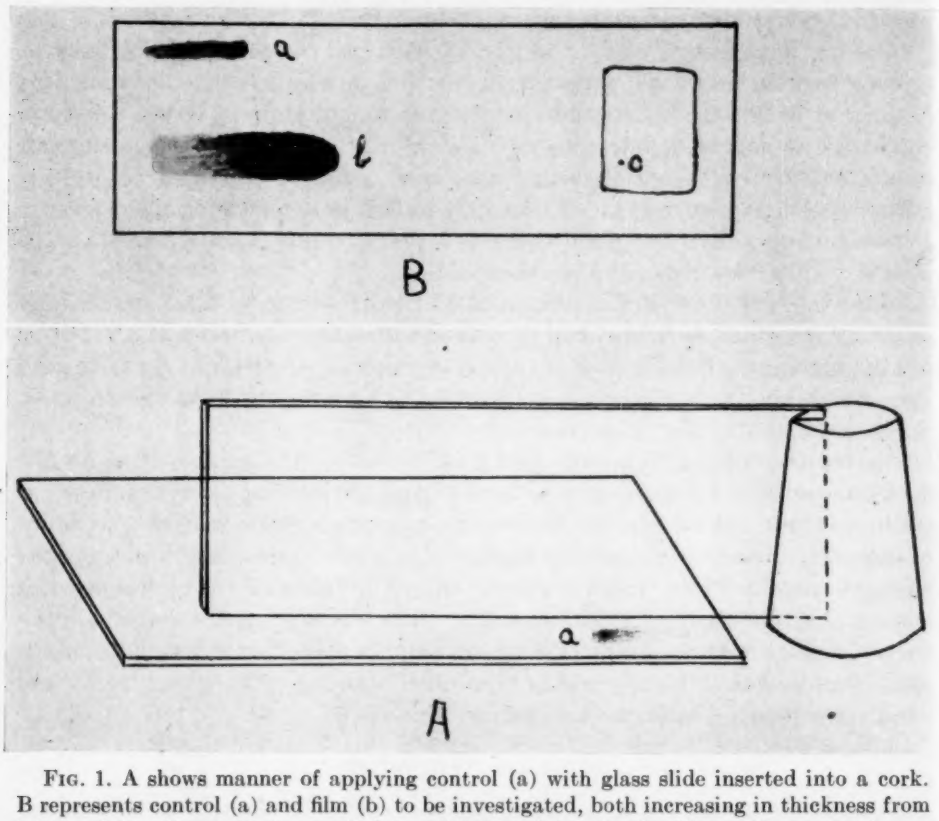

FIG. 1. A shows manner of applying control (a) with glass slide inserted into a cork. B represents control (a) and film (b) to be investigated, both increasing in thickness from left to right. C represents pencil dot on label at right, for identifying the area to be examined.

thin, the other is overthick. Between the two ends will be found a portion of optimum thickness. In case the material is known to be negative or to contain only a few organisms, we employ dilution-flotation (3). These films are made about 2 cm. long by 0.5 cm. wide. The manner of applying control and film is shown in figure 1B.

Staining: The stain is made stronger than the classical formula:

Fuchsin basic-crystals	12 g.
Alcohol 99 per cent	120 cc.
Phenol	50 cc.
Water to make	1,000 cc.

Stain for fifteen minutes on top of closed water bath at 65°C. Cool two to three minutes. Apply 3 per cent hydrochloric acid for thirty seconds. Wash with 70 per cent alcohol for ten seconds. Complete decolorization with 5 per cent freshly made sodium sulphite alternating with 70 per cent alcohol if necessary. Wash. Counterstain with picric acid 1/3 saturated for ten seconds. Still better results in stain penetration are obtained by the use of 15 g. fuchsin, and 150 cc. of alcohol, 50 cc. phenol and water to make 1,000 cc.

Since some fuchsin crystals[2] obtained in the market are inferior, each lot should be tested for stain penetration before using.

CRITERIA FOR JUDGING THE ADEQUACY OF THE CONTROL

According to the degree to which the organisms receive and retain the fuchsin dye, they are classified as deeply stained, well stained, or pale. Deeply stained organisms are broad, mostly with parallel sides, and the granules if present are completely masked by the intense staining of the bacillary bodies. Well stained organisms are less intensely stained, usually narrower and the granules are in evidence often projecting beyond the body wall giving a ragged or wavy cell-outline. Pale organisms appear as narrow pale pink threads, with or without granules. A well known variant shows one or more large granules with pale hair filaments attached. These variants are classified as well stained or pale, depending on the width of the body of the organism. Figure 2 illustrates these various well known types: deeply stained (2A); well stained (2B); and pale (2C).

Figures 2D, 2E and 2F represent drawings from the same field after light, moderate and deep staining. There are 11 pale granule form organisms and one doubtful organism *k* in 2D; *k* proves to be a definite organism on moderate staining in 2E; there are 4 deeply stained, 7 well stained and one pale organism in the field; *f* has lost the granule observed in 2D (*f*). On deep staining (2F), all organisms are deeply stained except *c*, which is well stained. A new organism not found in 2D and 2E is present; *l* appears as possibly 2 bacilli arranged end to end; *j* which terminated in line with *i* in 2D and 2E is prolonged downward in 2F in line with *h*. This indicates that there was an invisible portion of *j* which was demonstrated only on deep staining.

Summarizing the findings as to stain penetration the differentials are for 2D, $0 - 0 - 11 (+ 1 ?)$; for 2E, $4 - 7 - 1$; and for 2F, $12 - 1 (+ 1 ?) - 0$. This gives a certain gain of 2 organisms for deep staining over light staining or a percentage gain of 18 per cent. This simple method of observing the behavior of individual organisms under various degrees of stain penetration has been repeated in several other fields with similar results.

In examining the control, 30 single organisms found only in the thinnest portions are classified. Groups of organisms are ignored. Frequently every organism observed is deeply stained, but more often well stained organisms and an occasional pale organism are found. Well stained organisms are only slightly less visible than deeply stained, but their presence in considerable percentage

[2] In fifteen years' experience with the uncertified crystals obtained from the Coleman & Bell Co., we have found but a single inferior product.

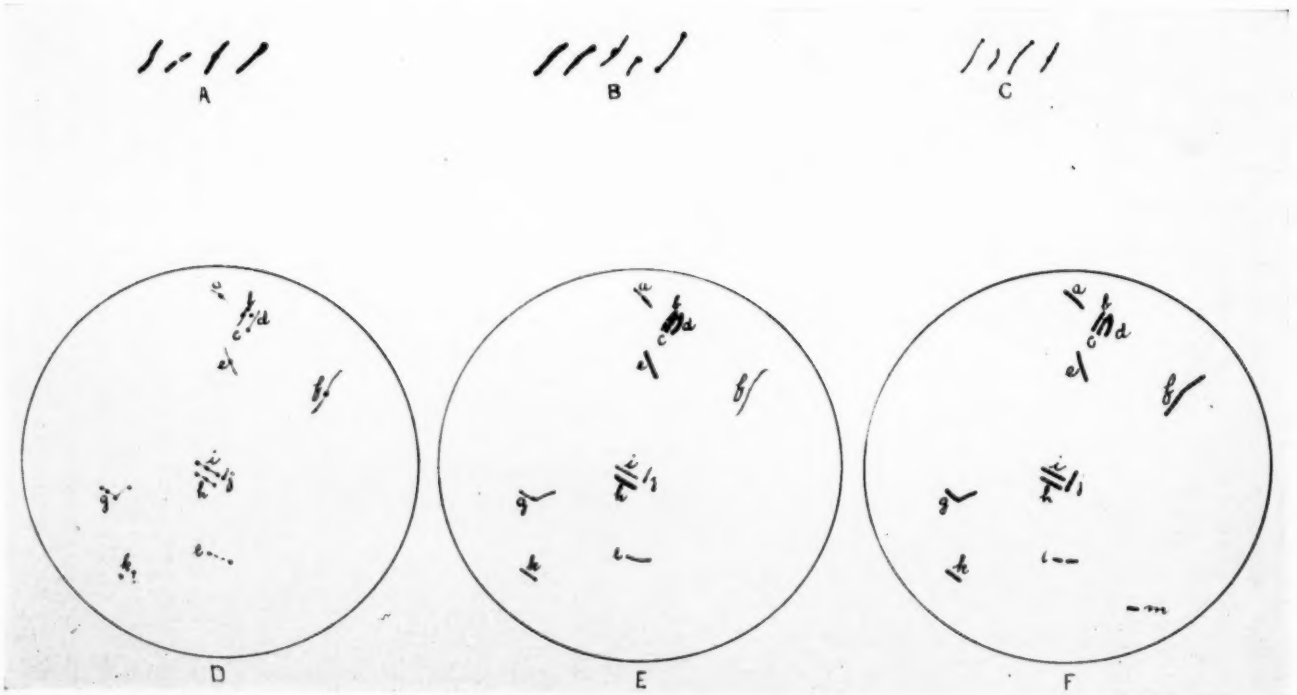

FIG. 2. A shows deeply stained organisms; B, well stained; and C, pale. D, E and F represent the same field stained lightly, moderately and deeply, respectively

indicates the presence of pale organisms (figure 2E), some of which are on the border of visibility and others may not be visible at all. Consequently we have required that at least 70 per cent of all organisms observed be deeply stained and that pale organisms shall not exceed 10 per cent. The lowest differential value for stain penetration permissible under this requirement is 21 deeply stained, 6 well stained, and 3 pale organisms, recorded 21 − 6 − 3. Little difficulty has been met in attaining this standard. Of 500 consecutive controls, restaining was necessary in 47 instances, or 9.4 per cent.

In practical procedure it is not necessary to make a differential of 30 organisms. In making the records by two observers, table 1, the first 12 organisms were differentiated and recorded separately and compared with the final result obtained with 30 organisms. The differentials 12 − 0 − 0, 11 − 1 − 0, 11 − 0 − 1, 10 − 2 − 0, and 10 − 1 − 1, were made in 89 of the 100 films, and indicated without exception that 70 per cent or better of deeply stained organisms were present. A record is also made of the number of organisms with prominent granules (figure 2D); these are rarely found in properly stained preparations except in the deeper layers of the film.

HAZARD OF CONTAMINATION OF THE UNKNOWN BY THE CONTROL

Since the placing of a positive control on the same slide with the unknown challenges the academic objection of possible contamination, the results of experience with the method are presented. The method has been tested with two different classes of materials. The identity of all stained films was unknown until the reports were made.

Reports made from the examination by dilution-flotation of the spleens and lymph nodes of 500 supposedly negative guinea pigs showed 4 positives. All of these guinea pigs failed to react to repeated tuberculin tests, and all clinical evidence and gross autopsy findings were negative. One of the positives was undoubtedly a contamination occurring at an earlier stage of the investigation, as two independent films were both positive. A single organism was reported in each of the 3 films remaining. Assuming that these 3 positive reports were false due to contamination from the control the probability of contamination is 3 in 500 or $\frac{1}{167}$. Applying this probability to sputum examination, in which 15 examinations are made per patient and adding the requirement that rare organisms must be found in three different specimens before a diagnosis is allowed, the probability of making a false diagnosis in the individual patient is expressed by $(\frac{1}{167})^3 \times \frac{15}{3} = \frac{1}{931493}$. One false positive report in 931,493 patients does not constitute a great hazard and such scant findings appropriately call for confirmation by guinea pig and culture.

The second test of the method is provided by the reports from the examination of films from 17 nontuberculous materials, each for one hour. These films were examined over a two-year period. One or more were mixed with batches of films which were known to contain rare findings. Each film (identity unknown) was examined for one hour, or less if three organisms were found. These 17 films were totally negative except one in which a single organism was reported.

Since a ten-minute search of films is employed routinely, there would be 102 ten-minute periods in the series, one of which is positive. Assuming contamination from the control in this case, the probability is $\frac{1}{102}$.

From these records we conclude that the chance of contamination from the positive control is very small, and that the academic objection to its use is far overrated in importance, in view of the marked improvement in results obtained.

ACCURACY OF THE CONTROL DIFFERENTIAL

The dependability of the control differential has been tested in several ways: first, by comparing two reports by the same observer on the same preparation at different times, the identity of the preparation being unknown until after the reports were made; second, by comparing the reports made by two observers on the same control; third, by comparing differentials of the control and positive films under investigation; and fourth, by comparing differentials of the control

TABLE 1

Showing dependability of the control differential under various conditions

	NUMBER OF FILMS	AVERAGES IN PER CENT						PROBABLE ERROR	
		1st			2nd				
		*d-s	w-s	p	d-s	w-s	p	d-s organisms	Percentage
Same observer two readings of control..	100	88.3	11.	0.7	88.7	10.7	0.6	±2.73	±3.1
Two observers independent readings...	100	88.3	11.	0.7	87.7	12.	0.3	±2.93	±3.3
Same observer control versus unknown.	100	80.1	18.6	1.3	82.4	16.3	1.3		
Same observer control fresh versus old..	180	87.8	11.4	1.3	80.5	18.2	1.3		

* d-s = deeply stained; w-s = well stained; p = pale.

when fresh and after being in use for a month or longer. Table 1 gives a summary of these comparisons.

The averages of first and second differentials made by the same observer from 100 films are almost identical, and the averages for two observers are only slightly less dependable. The probable error for deeply stained organisms calculated from the differences in first and second differentials is ±2.73 or ±3.1 per cent for the same observer and ±2.93 organisms or ±3.3 per cent for two observers. Such errors are well within the average error for blood counting.

The differentials made from both control and film show a slightly higher value for the latter. This value would be still greater were it not for the difficulty in making the films sufficiently thin. They average considerably thicker than the control, consequently are not stained at maximum penetration.

The table shows a diminution in stain penetration with the age of the control. This, however, is an advantage since a reading for the aging control indicates that a better reading will likely be obtained for the unknown. The averages given for the control, fresh versus old, are computed from the averages of the first twenty and last twenty readings of each of 9 different controls. Each of the 9

controls showed a decrease of stain penetration with age. The average time for the use of a control was sixty-seven days.

EVALUATION OF CONTROLLED STAINING

Films were made from various specimens of sputum, urine and tissue from guinea pigs, containing less than one bacillus in two fields. Some were prepared by direct smear; others by dilution-flotation. The positive control was streaked in the opposite corner of the slide. Films and control were purposely understained for forty-five seconds to one minute at 65°C. A stain penetration differential was made of both control and film. A suitable portion of the film was selected for counting in line with a pencil dot placed on the label at the right. Employing the mechanical stage the dot centered in the field of the low objective establishes the portion of the film to be searched. Beginning at the left border of the film a ten-minute count of organisms was made. The oil was then removed with xylene and ether, and the preparation was restained for fifteen minutes at 65°C. Various counterstains, picric acid, methylene blue 0.1 per cent and .005 per cent, brilliant green 0.1 per cent and .005 per cent were used, but the same dye and strength of dye were used on the same film for comparison of light and deep stain penetration. The control and film differential and a ten-minute count of organisms were repeated starting at the same point and proceeding over the same area as before.

The number of organisms found in a ten-minute count by each of the two methods of staining were then compared by dividing the larger by the smaller. This number represents the ratio of superiority of the technique giving the greater number.

Table 2 gives the comparative data for light and deep staining of 70 controls. Ten of these controls failed to meet the minimum requirement of 70 per cent of deeply stained organisms. A second stain was not attempted because of likelihood of losing the film by peeling. The average differential for light staining expressed in percentage is 10 — 67 — 23, which is far below minimum requirement. The average differential for deep staining is 81 — 17 — 2, which is well above the requirement. Note the decrease in granule form of organism from an average of 2.9 per cent to 1.4 per cent on deep staining. Although care was taken to stain all specimens exactly in the same way, using the same staining solution, a marked variation in stain penetration resulted for both light staining and deep staining. This confirms our belief that no mechanical plan will insure a dependable result and that controlled staining is necessary.

We anticipate criticism of the ratio of superiority for controlled staining given in table 3 on the ground that a purposely selected inferior technique is not a suitable basis for comparison. It is with full assurance, however, that the light staining as described is representative of much of the staining that is carried out in practice. In an unpublished survey of staining methods in 21 institutions throughout the country, it was found that 40 of 137 films submitted rated below the average for light staining, 10 — 67 — 23, in table 2, and 107 of the 137 films rated below the maximum for light staining, 37 — 58 — 5.

Restaining of preparations is associated with some difficulties of which loss of film in peeling is most important, especially in films prepared by concentration. This occurred in two films prepared by dilution-flotation so that an adverse ratio resulted. Difficulty in decolorizing is sometimes observed, resulting in an undesirable color tone. Dust particles are often increased on restaining. All these difficulties work to the disadvantage of the restain, so that the ratio of

TABLE 2

Comparison of stain penetration differentials made on 70 controls after light staining and deep staining

		DIFFERENTIAL EXPRESSED IN PERCENTAGE			GRANULE FORMS OF ORGANISMS
		*d-s	w-s	p	
Light staining 45 sec. to 1 min. at 65°C.	Minimum	0	38	62	0
	Maximum	37	58	5	11
	Average	10	67	23	2.9
Deep staining 15 min. at 65°C.	Minimum	30	60	10	0
	Maximum	95	5	0	0
	Average	81	17	2	1.4

* d-s means deeply stained; w-s, well stained; and p, pale.

TABLE 3

Comparison of results obtained by light staining and deep staining of 70 different preparations

	NUMBER OF FILMS	LIGHTLY STAINED FILMS							DEEPLY STAINED FILMS							
		Average							Average							
		Differential percentage						Organisms in 10-min. search	Differential percentage						Organisms in 10-min. search	Ratio superiority
		Control			Film				Control			Film				
		*d-s	w-s	p	d-s	w-s	p		d-s	w-s	p	d-s	w-s	p		
Negative:														*		
Direct smear	6	7	53	40				0	80	17	3	25	38	37	16	
Dilution-flotation	16	7	64	33				0	73	23	4	43	57	0	7	
Positive:																
Direct smear	17	17	70	13	14	76	10	21	90	10	0	73	25	2	46	3.14
Dilution-flotation	31	10	67	23	9	46	45	27	80	17	3	50	43	7	71	8.39

* d-s means deeply stained; w-s, well stained; and p, pale.

superiority for controlled staining as given in table 3 would be greater if the conditions found in initial staining could be maintained on restaining.

Table 3 gives a summary of results found by light and deep staining of the 70 preparations. Only 48 were positive in lightly stained films while all were positive in deeply stained films, representing an increase of 46 per cent. Considered negatively, of 70 positive films, light staining failed in 22, or 31 per cent. In direct smears it failed on the average in films in which the organisms were

present to the extent of 16 in a ten-minute search; in films prepared by dilution-flotation it failed on the average when they were present to the extent of 7 in a ten-minute search.

It should be noticed that the average percentage differentials for the films are less than the averages for their controls. This is due to the greater thickness of the films.

The ratio of superiority for deep staining in films prepared by dilution-flotation is much greater than in those prepared by direct smear. The ratios are 8.39 and 3.14, respectively. The probable reason for this is that the chemical reagents employed in dilution-flotation interfere somewhat with stain penetration, especially in those films stained lightly; deep staining overcomes this difficulty.

SUMMARY AND CONCLUSIONS

Experiments with controlled staining of *Mycobacterium tuberculosis* are presented and the method is advocated.

Of a total of 70 specimens containing few organisms only 48 were positive by light staining; all were positive by deep staining, representing a gain of 46 per cent.

The use of the positive control enables one to determine within a few seconds of time whether a film is properly stained.

The hazard of contamination from the positive control placed on the slide with the unknown is much overrated and the academic objection to its use is entirely unjustified in view of the marked increase in positive results obtained.

SUMARIO Y CONCLUSIONES

Después de presentar experimentos relativos a la coloración fiscalizada del *Mycobacterium tuberculosis*, recomiéndase esta técnica.

De 70 ejemplares que contenían pocos microbios, sólo 48 resultaron positivos con una coloración ligera; todos lo fueron con la coloración profunda, lo cual representa un aumento de 46 por ciento.

El empleo de un control positivo capacita para determinar en pocos segundos si una película está o no debidamente teñida.

Se ha exagerado demasiado el peligro de contaminación procedente de un testigo positivo colocado en la misma película que la incógnita, y está absolutamente injustificada la objeción teórica a su empleo en vista del decidido aumento que se obtiene así en los resultados positivos.

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COUNTERSTAINS IN DEMONSTRATING MYCOBACTERIUM TUBERCULOSIS IN SPUTUM[1]

JOSEPH E. POTTENGER

Many modifications of the Ziehl-Neelsen method of staining acid-fast organisms have been proposed. Some of these modifications are concerned with the strength and method of application of the primary stain; others are concerned with the strength and application of various decolorizing reagents; while still others offer some dye as a substitute for the methylene blue counterstain.

Spengler (1) modified the primary stain and introduced picric acid as a substitute for methylene blue. He frequently obtained positive results in material which was negative when methylene blue was used.

Konrich (2) recommended malachite green as a substitute for methylene blue, but did not compare results obtained by the two methods. Sodium sulfite was employed as a decolorizer.

Schulte-Tigges (3) modified Konrich's procedure by using picric acid as a counterstain. He found many more organisms than were found when methylene blue was used. Schoub (4), in comparing the Ziehl-Neelsen and Schulte-Tigges methods, reported 5.57 times as many organisms by the latter method. He considers that the picric acid counterstain is a responsible factor and that the sulfite in clarifying contributes to the result.

Cooper (5) modified the primary stain by adding salt solution, followed by brilliant green as a counterstain. This modification gave nearly 4 times as many organisms per field as were obtained by Ziehl-Neelsen.

Gardner (6) working with tuberculous pus from bone and joint lesions found the organisms in 90 per cent of specimens when counterstained by picric acid. Three-fourths of the specimens required but one to five minutes' search. He observes, "The counterstain is more important than is usually believed. Strong blue or green stains (1 per cent watery solutions) must never be used." He recommended one-half saturated picric acid or malachite green in faint tint. Shunker (7) working with sputum confirmed Gardner's opinion as to choice and use of counterstain.

Mills and Kendrick (8) compared the Ziehl-Neelsen and Schulte-Tigges methods on 700 specimens of sputum and, while the latter gave about one-fourth more organisms per field than the former, a sufficient advantage was not indicated to justify change of procedure. Simmons and Steves (9) made a similar comparison on 500 specimens of sputum, with conclusions in agreement with those of Mills and Kendrick.

Barnhart and Eberson (10) desiring to retain methylene blue recommended yellow light.

Bogen and Bennett (11) failed to find any more organisms per field by picric acid than by methylene blue.

Most of the above references indicate in different degrees that the methylene blue contrast, as originally employed, is not ideal. The general conclusion is that the lighter contrasts obtained by green or yellow give superior results. Some of these authors, in altering both the primary stain and counterstain, leave the question in doubt as to how much of the observed superiority is due to the particular counterstain employed.

[1] From the Laboratory of the Pottenger Sanatorium, Monrovia, California.

Since there are many variable factors contributing to the final results, due to the number of individual steps proposed, it may be readily understood why there has been much confusion in attempting to evaluate the various counterstains and staining techniques. Independently there are those who hold that no important advance has been made beyond the results to be obtained by the Ziehl-Neelsen method.

After thirty years' experience with picric acid as a counterstain and having observed repeatedly its striking superiority over methylene blue, it is believed that most of the confusion referred to is to be attributed to failure to comprehend the importance of the counterstain. This belief is further strengthened by failure to find a single article in the literature dealing with the counterstain *per se*. Other factors being constant, it seems that the effect of the various counterstains on visibility may be readily determined by quantitative methods. This is attempted in the following experiments.

TECHNICAL PROCEDURE

Selection and preparation of material: Six sputa containing from one to three bacilli per field, showing wide variations in content of protein, pus, epithelium, bacteria and dust cells, were selected for study.

The sputa were shaken by mechanical shaker for twenty to forty minutes depending upon the viscosity of the material, to secure uniform distribution of the organisms. Strongly purulent sputa were diluted with equal parts of 0.6 per cent sodium chloride before shaking. From fractions of these homogenized sputa, secondary dilutions were made (1/4, 1/16 and 1/64 original strength) and shaken for fifteen minutes. A series of precision slides[2] sterilized at 200°C. were placed on a plate glass platform and leveled by spirit level, over a drying oven at 65°C. Exactly 1 cc. of each dilution was placed on each of two slides. The material spread spontaneously and dried in about twenty minutes. On one of each pair of slides was placed another cubic centimetre of the same dilution. In this way a series of films was made from 1/64, 1/32, 1/16, 1/8, 1/4, and 1/2 dilution and the original sputum, each dilution representing one-half the thickness of the next succeeding dilution.

Standardization of films: Due to marked variation in content of the various elements in different sputa, it was considered that thickness of the various preparations might be most accurately expressed in terms of total nitrogen content. A Kjeldahl determination was made on each sputum expressed in grams of nitrogen per 100 cc., from which the theoretical quantity of nitrogen for each of a series of dilutions was determined. Table 1 gives a quantitative comparison of protein, cell volume and nitrogen expressed in percentage and an estimate of percentages of neutrophils, lymphocytes and epithelium in the six sputa. The number of bacteria and dust cells are also indicated. The parallelism between cell volume and nitrogen is close; the figure for cell volume being about twenty times the figure for nitrogen for each sputum. The figures for protein are not so closely related.

Staining and counting: The slides were completely covered with carbol fuchsin for five minutes at 65°C. After pouring off the stain they were covered gently with 5 per cent sulfuric acid for thirty seconds. They were then carefully immersed in a beaker of water

[2] Precision slide is the trade name for specially ground slides having flat and parallel surfaces.

until no more stain came away. Complete decolorizing was accomplished by Osol's method (12), consisting of 5 parts 10 per cent sodium sulfite and 1 part 96 per cent alcohol. The sulfite was removed by prolonged immersion in a beaker of water. In the thicker films additional applications of sulfite were necessary. The various counterstains, strength and time of application were selected to cover the probable extremes employed in practice: methylene blue 1 per cent 30 seconds, 0.1 per cent thirty seconds, and 1/150 per cent one minute; bismarck brown 1 per cent two minutes, and .05 per cent one minute; picric acid 1 per cent five to ten seconds, malachite green one-third saturated, one minute and .02 per cent one minute.

TABLE 1

Showing physical and chemical characteristics of six sputa used in studies on comparative value of counterstains

SPUTUM	ESTIMATED					QUANTITATIVE DETERMINATION EXPRESSED IN PERCENTAGE		
	Percentage cell elements			Per field		Protein	Cell volume	Total nitrogen values
	Neutrophils	Lymphocytes	Epithelium	Bacteria	Dust cells			
A	95	3	0	Few	0	.35	10.8	.55
B	90	9	1	Many	1 per field	.5	8.3	.412
29203	90	9	2	Numerous	1 per field	.15	5.2	.329
29246	70	30	10	Numerous	Occasional	.15	5.0	.25
29292	90	8	1	Many	Occasional	.35	8.1	.424
29325	80	18	20	Numerous	Occasional	.15	3.4	.19

FIG. 1. Showing application of counterstains to stained films. Dotted lines are 2 cm. from end of slide.

The application of the counterstains to the film is shown in figure 1. Beginning 2 cm. from the end of the slide, an area 0.5 cm. by 0.2 cm. was covered with a drop of each dye by means of a finely pointed capillary pipette, the time of exposure accurately determined and the excess dye removed carefully with a clean cloth. Three counterstains were applied in this way, parallel to each other, close to the long axis of the slide. In order to neutralize the slight advantage in thickness in the central portion of the film each counterstain was given this position in rotation. A ten-minute count of organisms was made for each counterstain.

Probable error of the counting method: In order to determine the probable error of the counting method, two five-minute periods were tabulated separately and

the percentage variation was expressed in terms of the lower count. A total of 118 comparisons were made distributed almost equally among the various counterstains. The percentage variations were occasionally huge in the extreme dilutions, when both five-minute counts were less than 20 organisms. There were 51 of these counts, giving a probable error for a five-minute count of ±60.7 per cent, which for a ten-minute count would be ±42.9 per cent. In 67 counts in which both five-minute counts exceeded 20 organisms, the probable error was ±10.1 per cent for a five-minute count or ±7.1 per cent for a ten-minute count. Since most of the counts given in table 2 exceed 40 organisms it seems that the result for a ten-minute count is dependable within a reasonable degree of error.

Table 2 shows the relative value of each counterstain, in each dilution of each of the six sputa. In the first column under each counterstain is recorded the number of organisms found in a ten-minute search. Since methylene blue 1 per cent is the strength generally employed, it is accepted as the base for computing relative values, with a rating of 1. All other counterstains are compared with the base by dividing the number of organisms found by the number found with methylene blue 1 per cent. This ratio expresses the relative value of the counterstain for that particular dilution These ratios are found in the second column under each counterstain.

Of 252 comparisons of the various counterstains in table 2 methylene blue 1 per cent gave greater counts in only 7 instances. Since all but one of these counts occurred when both counts were under 30 organisms, it is assumed that improper distribution of organisms was the cause of the adverse results.

In table 3, three ratios of superiority are given for each counterstain. Number 1 represents the average of all ratios determined for each dilution; number 2 represents the ratios computed from the total of all organisms found for each counterstain; and number 3 represents the ratios computed from the total of the highest counts obtained in each of the six sputa for each counterstain regardless of the dilution. In practice the last series of ratios is the correct one, since each counterstain is rated according to its best performance.

It is significant that each of the series of ratios places picric acid as the most efficient, no counterstain second, and methylene blue 1 per cent least of all. The preferred series of ratios (no. 3) shows picric acid to be 6.2 times, no counterstain 4.8 times, and methylene blue $\frac{1}{150}$ per cent, 4.5 times more efficient than methylene blue 1 per cent.

The failure of 1 per cent methylene blue results from two conditions: in thin films, the cellular elements and bacteria are stained so deeply that rapid search is impossible; in thick films the stain is more intense so that the organisms are masked resulting in decreasing counts with increase in thickness of films. Methylene blue 0.1 per cent is slightly better than methylene blue 1 per cent but similarly objectionable. Even in the dilution of $\frac{1}{150}$ per cent, bacteria are sufficiently stained to interfere with rapid search. Malachite green, though not as intense a stain as methylene blue, is objectionable to a less degree. Bismarck brown is objectionable because of poor color contrast.

Figure 2 shows the relative efficiency of the various counterstains. The

shaded bars represent the superiority ratios from table 3 (number 2) computed from the total number of organisms found for each counterstain (table 2) and

TABLE 2

Showing relative value of counterstains in films made from serial dilutions of six sputa

SPUTUM	TOTAL NITROGEN, GM. PER 100 CC.	COUNTERSTAINS USED																NO COUNTERSTAIN	
		Methylene blue						Malachite green				Bismarck brown				Picric acid			
		1%		$\frac{1}{10}$%		$\frac{1}{150}$%		$\frac{1}{3}$ saturated		$\frac{1}{50}$%		1%		$\frac{1}{20}$%		1%			
		10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio	10-minute count	Superiority ratio
A	.014	10	1	7	0.7	16	1.6	7	0.7	20	2.0	9	0.9	12	1.2	31	3.1	16	1.6
	.028	24	1	14	0.7	27	1.3	32	1.5	42	2.0	42	2.0	36	1.7	64	3.0	43	2.0
	.056	30	1	46	1.5	78	2.6	83	2.8	84	2.8	87	2.9	85	2.8	136	4.5	100	3.3
	.112	73	1	85	1.2	107	1.5	108	1.5	117	1.6	120	1.6	135	1.8	196	2.7	115	1.6
	.224	44	1	105	2.4	235	5.3	97	2.2	165	3.7	105	2.4	212	4.8	277	6.3	270	6.1
B	.006	52	1	53	1.0	51	1.0	75	1.4	111	2.1	76	1.5	116	2.2	128	2.5	144	2.8
	.013	39	1	50	1.3	85	2.2	90	2.3	131	3.4	80	2.0	146	3.7	188	4.8	168	4.3
	.026	42	1	49	1.8	105	2.5	81	1.9	245	5.8	126	3.0	193	4.6	290	6.9	220	5.0
	.051	69	1	81	1.2	400	5.8	163	2.4	295	4.3	97	1.4	190	2.7	580	8.4	302	4.4
29203	.041	0	1	1	1.0	3	3.0	4	4.0	5	5.0	1	1.0	4	4.0	4	4.0	3	3.0
	.082	1?	1	1	1.0	5	5.0	3	3.0	9	9.0	5	5.0	7	7.0	9	9.0	8	8.0
	.164	1	1	1	1.0	5	5.0	8	8.0	7	7.0	5	5.0	5	5.0	5	5.0	9	9.0
29246	.004	1	1	2	2.0	3	3.0	4	4.0	3	3.0	2	2.0	4	4.0	6	6.0	7	7.0
	.008	5	1	5	1.0	2	0.4	6	1.2	11	2.2	10	2.0	10	2.0	15	3.0	11	2.2
	.016	9	1	8	0.9	8	0.9	19	2.1	19	2.1	15	1.7	15	1.7	25	2.8	19	2.1
	.032	19	1	16	0.8	26	1.4	21	1.1	35	1.8	32	1.7	32	1.7	43	2.3	41	2.2
	.064	16	1	26	1.6	54	3.4	67	4.2	74	4.6	53	3.3	101	6.3	106	6.6	92	5.7
	.128	15	1	28	1.9	51	3.4	58	3.9	68	4.5	74	4.7	140	9.3	119	7.9	144	9.6
	.256	3	1	12	4.0	74	24.7	93	31.0	97	32.0	14	4.7	92	30.7	105	35.0	120	40.0
29292	.006	8	1	12	1.5	14	1.7	17	2.1	22	2.7	18	2.5	25	3.1	28	3.5	19	2.4
	.013	26	1	17	0.6	28	1.1	22	0.8	36	1.4	32	1.2	49	1.9	71	2.6	47	1.8
	.026	67	1	55	0.8	101	1.5	66	1.0	105	1.6	109	1.6	86	1.3	147	2.1	97	1.4
	.052	60	1	61	1.0	129	2.1	146	2.4	195	3.2	132	2.2	176	2.9	202	3.4	166	2.8
	.104	68	1	106	1.6	266	4.0	200	3.0	265	3.9	170	2.5	257	3.8	376	5.5	350	5.4
	.208	16	1	145	9.0	323	20.2	288	18.0	335	20.9	173	10.8	301	18.8	434	27.1	376	23.5
29335	.095	1	1	2	2.0	7	7.0	6	6.0	3	3.0	11	11.0	5	5.0	15	15.0	12	12.0
	.190	3	1	4	1.3	12	4.0	15	5.0	10	3.3	6	2.0	15	5.1	16	5.4	19	6.3
	.380	1	1	2	2.0	14	14.0	14	14.0	10	10.0	16	16.0	9	9.0	10	10.0	7	7.0

the unshaded extensions represent the increased superiority computed from the highest count for each counterstain from each sputum, regardless of dilution.

Figure 3 shows the comparative value of 1 per cent methylene blue and picric acid on the basis of the total number of organisms found with each counterstain in 4 of the sputa (table 2) for each total nitrogen value. At the bottom of the

TABLE 3

Showing superiority ratios of counterstains in comparison with 1 per cent methylene blue, computed from data in table 2

SUPERIORITY RATIOS COMPUTED FROM TABLE 2	COUNTERSTAINS USED								NO COUNTERSTAIN
	Methylene blue			Malachite green		Bismarck brown		Picric acid	
	1%	1/10%	1/100%	1/3 saturated	1/30%	1%	1/10%	1%	
Ratio:									
No. 1. Average ratios	1	1.7	4.6	4.7	5.3	3.5	5.3	7.1	6.5
No. 2. Based upon total organisms found	1	1.2	2.8	2.2	3.1	2.0	3.1	4.5	3.5
No. 3. Based upon sum of highest counts for each counterstain in each sputum	1	1.6	4.5	2.6	3.9	2.2	3.7	6.2	4.8

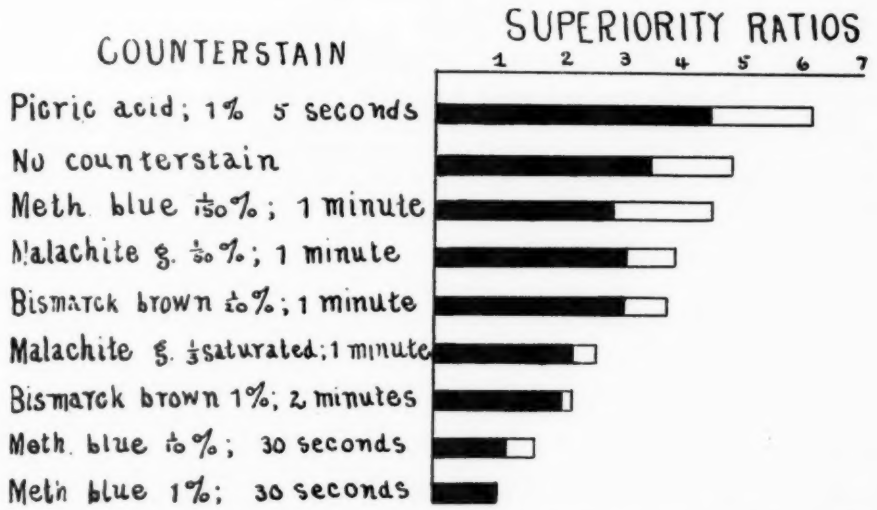
COUNTERSTAIN
SUPERIORITY RATIOS
1 2 3 4 5 6 7
Picric acid; 1% 5 seconds
No counterstain
Meth blue 1/150%; 1 minute
Malachite g. 1/30%; 1 minute
Bismarck brown 1/10%; 1 minute
Malachite g. 1/3 saturated; 1 minute
Bismarck brown 1%; 2 minutes
Meth blue 1/10%; 30 seconds
Meth blue 1%; 30 seconds

FIG. 2. Showing superiority ratios of each counterstain computed by two different methods. The shaded bars represent the total number of organisms found for each counterstain. The unshaded extensions represent increased ratios computed on the basis of the sum of the highest counts found in all sputa for each counterstain.

figure is given the ratio of superiority of picric acid for each total nitrogen value. Note that 1 per cent methylene blue reaches its maximum at total nitrogen .056, decreasing as thickness of film increases. Picric acid, on the other hand, increases up to and probably beyond total nitrogen .224. At total nitrogen .224

it gives a superiority ratio of 19.0 over methylene blue. At this point methylene blue is approaching the state of a complete "black-out" of organisms.

The relation of thickness of film to the count of organisms is of further interest. Referring to table 2, it is noticed that the count for each counterstain increases appreciably with increased thickness of film, up to a certain point, but this increase is not in proportion to the increase in number of organisms present, which

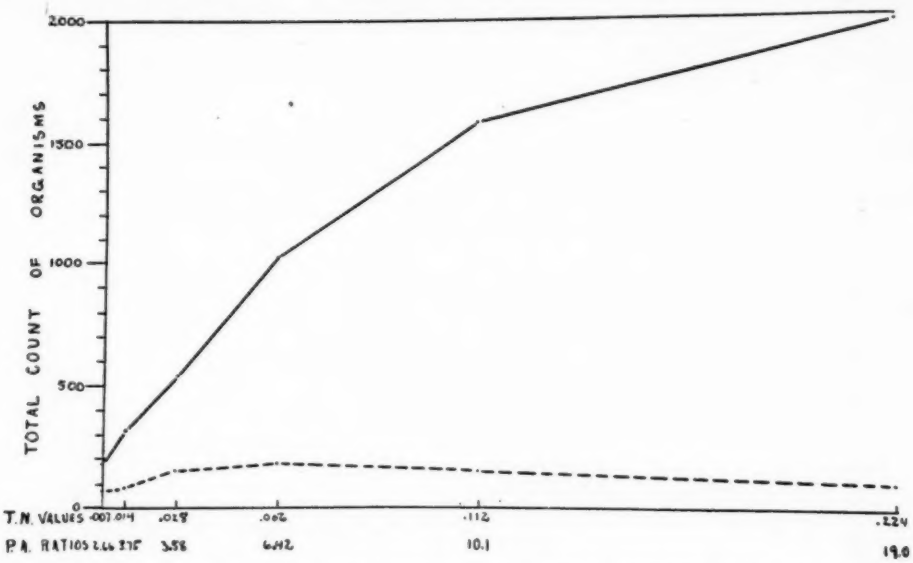

FIG. 3. Comparing picric acid and 1 per cent methylene blue in each of a series of stained films of increasing thickness. The broken line represents methylene blue and the solid line, picric acid.

TABLE 4

Showing total counts of organisms, theoretical and actual rates of increase of counts for each total nitrogen value

	TOTAL NITROGEN VALUES OF FILMS					
	.007	.014	.028	.056	.112	.224
Total organisms counted	725	1083	1881	3379	4933	6413
Theoretical rates of increase	1	2	4	8	16	32
Actual rates of increase	1	1.5	2.6	4.7	6.8	9

doubles with each succeeding film. This lag in count is due to time lost in focusing, the additional time required to count more organisms and the fact that the organisms in the lower film layers are understained. Table 4 gives a summary of all counts and the theoretical and actual rates of increase obtained with the lighter counterstains for each total nitrogen value.

It is difficult to make films thicker than total nitrogen .224 because of the tendency to peel, but such thickness is desirable in view of the increased counts ob-

tained and especially since the progressive increase in actual rates indicates that optimum thickness has not been reached for the lighter counterstains.

PROPER CRITERIA FOR THE EVALUATION OF STAINING TECHNIQUES

In the attempt to evaluate various staining techniques developed within the past fifty years, the usual method employed has been to compare the numbers of organisms found per field by the techniques being investigated, taking care that the films are of comparable thickness. Of the authors mentioned earlier, Mills and Kendrick, Simmons and Steves, Cooper, and Bogen and Bennett employed this method. Others, ignoring field comparisons, based their conclusions upon the relative number of organisms found after continuous search, and upon the greater number of positive films found by one method as compared with another.

TABLE 5

Comparison of counts of organisms by field and in five minutes' search in films counterstained by 1 per cent picric acid and 0.1 per cent methylene blue

5-MINUTE SEARCH	COUNTERSTAIN USED							SUPERIORITY RATIO	
	Methylene blue 0.1 per cent				Picric acid 1 per cent				
	Number of sputa	Fields counted	Total organisms found	Average organisms per field	Fields counted	Total organisms found	Average organisms per field	Field counts	Total bacilli
100 organisms or less.....	10	241	728	3.0	518	1,664	3.2	1.07	2.27
101 organisms or more.....	5	91	1,513	16.6	149	2,505	16.8	1.01	1.66

For thirty years we have made the time of search a part of the record when the films are negative or only a few organisms are found, such as "negative in ten minutes' search" or "7 organisms in ten minutes' search." As a result of this experience and experiments performed we are firmly convinced that the proper basis for comparing two techniques is the relative number of organisms found in a definite period of time by continuous search in films of optimum thickness for each counterstain.

In the following experiment both methods are taken into consideration. Films were made from 15 positive sputa homogenized and spread on precision slides as previously described. Some of the films were rather thin; others were moderately thick. After staining and decolorizing one-half of the film was counterstained with picric acid, the other half with methylene blue 0.1 per cent.

The sputa reported in table 5 were rather strongly positive and were selected to conform to the numbers of organisms reported by Mills and Kendrick and Simmons and Steves. They are separated into two groups according to the numbers of organisms found in a five-minute search with methylene blue counterstain. Group 1, comprising 10 sputa with counts of 100 organisms or less, and group 2, comprising 5 sputa with counts exceeding 100 organisms. Note that the count by fields is almost the same by the two methods in agreement with

the conclusion of the authors referred to; but of far greater importance is the greater number of fields counted when picric acid is used.

In group 1, based upon total organisms found, picric acid shows a superiority ratio of 2.27 over methylene blue; in group 2, a ratio of 1.66 is obtained, suggesting that the ratio increases with the decrease in the number of organisms present. It suggests further that the true superiority ratio of a method cannot be determined from the strongly positive films usually employed for comparison. Those films only which contain a few organisms in a ten-minute search are suitable for this purpose. A comparison of the sum of all counts of 30 organisms or less obtained with 0.1 per cent methylene blue with the sum of corresponding counts obtained with picric acid in table 2 gives $662 \div 148 = 4.47$. This ratio is almost double the ratio given for counts of 100 or less in table 4. Positive sputa in this low range of bacillary population are of extreme importance in diagnosis, and comparison of techniques should be confined to this range.

SUMMARY AND CONCLUSIONS

A comparison of eight different counterstains and no counterstain for the demonstration of *Mycobacterium tuberculosis* is presented.

The order of efficiency as shown by the number of organisms found in standardized films by each of the counterstains is picric acid, no counterstain, methylene blue $\frac{1}{150}$ per cent, malachite green .02 per cent, bismarck brown .05 per cent, malachite green one-third saturated, bismarck brown 1 per cent, methylene blue 0.1 per cent, and methylene blue 1 per cent.

Rated on the basis of best performance in a series of films of graduated thickness, picric acid gives 6.2 times as many organisms as methylene blue 1 per cent; no counterstain, 4.8 times as many; and methylene blue $\frac{1}{150}$ per cent 4.5 times as many.

The dark counterstains generally employed should be dispensed with and lighter tints employed if proper efficiency is to be attained in diagnosis.

The usual method of comparison by fields for the evaluation of staining techniques is fallacious, since it ignores the far more important factors of comparative results obtained in unit time of search and the particular thickness of film suited to each counterstain. The proper basis restricts comparison to films containing only a few organisms in a ten-minute continuous search, and the films should be of such thickness as will give the maximum result for each counterstain.

SUMARIO Y CONCLUSIONES

Compárase el resultado obtenido en la pesquisa del *Mycobacterium tuberculosis* con ocho distintos contracolorantes y sin contracolorante.

La eficacia, expresada por el numero de microbios encontrados en las películas estandardizadas con cada uno de los contracolorantes, confórmase a este orden: ácido pícrico; sin contracolorante; azul de metileno al 1/50 por ciento; verde de malaquita al 1/50 por ciento; pardo de bismarck al 1/20 por ciento; verde de malaquita al 1/3 saturado; pardo de bismarck al 1 por ciento; azul de metileno al 1/10 por ciento; y azul de metileno al 1 por ciento.

Tomando por base el mejor resultado obtenido en una serie de películas de espesor graduado, el ácido pícrico descubre 6.2 veces más microbios que el azul de metileno al 1 por ciento; la técnica sin contracoloración, 4.8 veces; y el azul de metileno al 1/50 por ciento, 4.5 veces más.

Deben eliminarse los contracolorantes oscuros empleados generalmente, y emplearse tintes más claros si va a obtenerse la eficacia debida en el diagnóstico.

El método habitual de comparación de los campos para avaluar las técnicas de coloración peca de falaz, puesto que desatiende otros factores mucho más importantes, o sean los resultados obtenidos en el mismo tiempo de investigación y con el espesor más apropiado a cada contracolorante. Esta base lógica limita las comparaciones a las películas que sólo contienen algunos microbios y son estudiadas continuamente por diez minutos, y son de tal espesor que cada contracoloración rinde el resultado óptimo.

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PRESENT PRACTICE IN STAINING MYCOBACTERIUM TUBERCULOSIS IN REPRESENTATIVE INSTITUTIONS[1]

JOSEPH E. POTTENGER

In order to check the results of our experience with controlled staining (1) of *Mycobacterium tuberculosis* it was considered advisable to ascertain the methods of preparation and staining employed in other institutions. It was further considered advisable to determine whether these preparations could be improved and to what degree by the method of controlled staining and the use of picric acid as a counterstain.

METHOD OF INVESTIGATION

A questionnaire for the purpose of securing information relating to technical procedure was sent to 23 institutions, and request was made for 5 routinely stained preparations ranging from one organism in 2 fields to 5 organisms per field.

When received the slides were labeled by an assistant with a number for the institution, and a different letter for each slide of the series, such as, 1a, 1b, 1c, *et cetera*. The slides from 3 or more institutions were intermixed. The identity of the institution and method of preparation were not known until after the observations were made.

Selecting the thinnest portions of each film, 100 organisms were classified as deeply stained, well stained or pale, according to a plan (1) previously described. Also an exact count of the number of bacilli found in a ten-minute search was made, a group of bacilli counting as one. The area of the film observed was determined by placing a pencil dot on the label at the right which was centered in the field of the low objective. Employing the mechanical stage, and starting at the left border after adjusting the immersion lens, the count was made from left to right. After completing the count the oil was removed with xylol and ether and the lower half of the preparation was restained for fifteen minutes on a closed water bath at 65°C. Observation as to stain penetration and count of organisms was repeated, starting at the same point as in the original film. The original count was then compared with the count from the restain by dividing the greater by the lesser. The quotient represents the ratio of superiority of the greater count.

An estimate of the relative thickness of each film was recorded on a scale, .1, .2, .3, *et cetera*, up to 1, figure 1 representing the optimum thickness when picric acid is used. Counterstains were recorded as light, medium and dark. Any peculiarity of a film which would influence visibility, such as "dust cells," dirt, *et cetera*, was recorded.

ANSWERS TO QUESTIONNAIRE

Number 1: In staining how do you guard against understaining of your preparations? Five state that no special measure is employed. Fifteen express the belief that the technique employed protects against understaining.

Number 2: Do you approve of staining a positive control placed on the same slide with the unknown? Six consider a positive control unnecessary, 3 favor its use, one expresses an open mind and 13 are strongly opposed to its use.

Number 3: Do you insist on the use of certified stains? Ten use them ex-

[1] From the Laboratory of the Pottenger Sanatorium, Monrovia, California.

clusively, 8 consider them unnecessary and 3 use both certified and uncertified stains.

Number 4: What digestant do you use for concentration? What strength? Eight use 3 to 6 per cent sodium hydroxide, 5 use the chemical flocculation method, 3 employ dilution-flotation and one each employs disodium phosphate with trypsin digestion, sodium bicarbonate followed by antiformin, autoclave, autoclave followed by 3 per cent hydrochloric acid and neutralized with 3 per cent sodium hydroxide, 5 per cent oxalic acid and 3 per cent hydrochloric acid.

Number 5: What is your method of staining? Thirteen steam the carbol-fuchsin for periods ranging from three to twenty minutes, 4 employ Cooper's method and 4 employ the cold method, ranging from forty-five minutes to twenty-four hours.

Number 6: What counterstain do you use? Thirteen use methylene blue from .02 per cent to Loeffler's full strength, 4 use brilliant green 0.1 to 1 per cent strength, 2 use picric acid, one uses fast green and one uses malachite green.

RESULTS OF INVESTIGATION

Material received: Twenty-one institutions sent 137 slides, 46 direct smears and 91 concentrated films. Thirty-two of the direct smears were counterstained with methylene blue, 9 with brilliant green, 3 with malachite green and 2 with picric acid. Of the specimens prepared by concentration, 53 were counterstained with methylene blue, 33 with brilliant green, malachite green, or fast green and 5 with picric acid.

Difficulties encountered: For quantitative comparison, several difficulties were encountered in restaining, such as failure to remove all traces of oil, increased difficulty in decolorizing, increase in dust particles and tendency of the film to peel. The latter outweighed all other difficulties and resulted in the loss of 12 films prepared by strong sodium hydroxide. No evidence of peeling was noticed in the films prepared by direct smear.

Table 1 gives a summary of results by institutions; minimum, maximum, and average stain penetration differentials are given for each group. If minimum and maximum for each institution are compared, the variation in most instances is marked, indicating that uniformity of stain penetration is not secured, as commonly supposed by uniformity of treatment in staining. There was only one group (institution No. 10) that gave averages of 70 per cent deeply stained. On restaining we obtained 70 per cent or better for all groups except No. 12 which was slightly under the requirement.

Table 2 summarizes the results obtained from 137 individual films. Only 8 of these films gave 70 per cent or better of deeply stained organisms, but on restaining we met this requirement in all except 3 films. Note the almost total disappearance of pale organisms in the restained film with marked diminution of well stained organisms. The granule form of organism decreased from 7.3 per cent to 0.9 per cent on restaining. The average estimate of thickness of the films was .44 and the average superiority ratio of the restained over the original films was 7.34.

TABLE 1

Summary of data in the examination of films from each institution

INSTITUTION	STAIN PENETRATION DIFFERENTIAL																AVERAGE	
	Original film												Restain					
	Number of films	Minimum			Granule forms	Maximum			Granule forms	Average			Granule forms	d-s	w-s	p	Granule forms	Superiority ratio	Thickness of film
		*d-s	w-s	p		d-s	w-s	p		d-s	w-s	p							
1	5	14	68	18	40	42	54	4	9	22	70	8	16.8	77	21	2	1.6	1.85	.4
2	5	0	27	73	85	3	41	56	12	1	47	52	61.0	77	23	0	0.8	6.4	.36
3	12	0	43	57	0	13	81	6	0	7	78	15	0.2	78	21	2	0.6	1.92	.47
4	5	4	75	21	15	37	58	5	5	12	74	14	9.0	80	17	3	1.6	2.73	.42
5	5	1	85	14	0	14	82	4	1	6	85	9	0.2	78	20	2	3.6	3.61	.48
6	5	9	86	5	0	69	30	1	0	49	49	2	0	90	9	1	0	†(4) 1.00	.3
7	8	15	76	9	0	71	29	0	0	34	63	3	0	86	13	1	0.6	4.57	.41
8	5	3	44	53	0	33	64	3	7	14	66	20	15.0	79	19	2	0.8	5.42	.34
9	8	35	62	3	0	58	40	2	8	51	46	3	6.0	78	21	1	0.3	(2) 1.34	.27
10	9	61	37	2	0	88	12	0	0	70	29	1	0	85	13	2	0.4	1.32	.43
11	5	0	0	100	1	13	79	8	8	4	39	57	6.0	75	19	6	5.0	(4) 57.5	.52
12	2	0	22	78	5	1	42	57	19	1	32	67	12	69	28	3	0	14.6	.6
13	10	16	54	30	5	71	24	5	0	40	52	8	0.5	81	17	2	0.3	4.38	.42
14	6	3	70	27	13	19	56	25	20	10	72	8	8	75	20	5	1.8	(5) 2.82	.69
15	5	3	85	12	0	40	60	0	0	26	68	6	0.6	85	13	2	0.6	4.37	.2
16	15	0	40	60	0	23	64	13	2	11	73	16	3.2	77	21	2	0.3	2.54	.41
17	5	3	74	23	2	70	30	0	0	27	61	12	1.4	76	22	2	0	5.35	.88
18	6	0	58	42	21	44	42	14	11	10	70	70	9	73	23	4	1.5	(3) 1.24	.37
19	5	4	82	14	0	57	38	5	0	25	67	8	2	75	20	5	0.4	24	.38
20	5	0	47	53	43	41	57	2	10	15	62	23	23.2	79	18	3	4.4	1.26	.28
21	6	0	32	68	28	8	83	9	15	4	58	38	19.7	78	18	4	2	1.37	.65

* d-s = deeply stained; w-s = well stained; p = pale.

† Numbers in parentheses express the number of films averaged; the remaining films of the series were lost by peeling.

TABLE 2

Summary of data from table 1 comparing the original and restained films

Averages

NUMBER OF FILMS	AVERAGE STAIN PENETRATION						GRANULE FORMS		THICKNESS OF FILM	RATIO OF SUPERIORITY OF RESTAIN OVER ORIGINAL FILM
	Original film			Restained film			Original	Restain		
	*d-s	w-s	p	d-s	w-s	p				
137	22.6	61.1	16.3	79.4	18.2	2.4	7.3	0.9	.44	†7.34

* d-s = deeply stained; w-s = well stained; p = pale.

† Only 124 ratios are averaged because of peeling of films in restaining.

Table 3 gives the ratios of superiority for restaining in comparison with the original films with reference to the intensity of the counterstain and to the number of organisms found in the original films in a ten-minute count. These

ratios increase with the intensity of the counterstain and decrease with the increase in the number of organisms, as was shown elsewhere (2). When the organisms are present to the extent of 500 or more in a ten-minute search, they can be counted readily regardless of the counterstain employed and the proper comparison is not found under such conditions.

From a diagnostic standpoint the first row of ratios from films yielding counts of 100 organisms or less is of special importance. In this range success or failure

TABLE 3

Ratios of superiority of restaining over original film

ORGANISMS IN 10-MINUTE SEARCH	INTENSITY OF COUNTERSTAIN							
	Direct smear				Concentration			
	Light	Medium	Dark	Combined	Light	Medium	Dark	Combined
100 bacilli or less	*(8) 5.34	(8) 5.83	(1) 8.8	(17) 5.77	(13) 2.66	(7) 34.7	(7) 22.1	(27) 16.01
101 to 500	(5) 2.58	(7) 2.71	(3) 4.34	(15) 3.0	(17) 1.66	(13) 3.23	(7) 3.93	(37) 2.65
501 or more	(4) 1.19	(8) 1.37	(1) 2.79	(13) 1.43	(5) 1.79	(6) 2.0	(4) 1.71	(15) 1.85

* Numbers in parentheses indicate the number of films from which the average is computed.

TABLE 4

Records of 8 inferior preparations

SLIDES	COUNTERSTAIN	STAIN PENETRATION								RATIO SUPERIORITY
		Original			Restain			10-minute count		
		*d-s	w-s	p	d-s	w-s	p	Original	Restain	
2a	†M.b. light	0	59	41	87	12	1	28	365	13.03
7h	B.g. medium	2	8	0	76	20	4	5	50	10.0
8c	M.b. dark	3	44	53	90	10	0	65	1,290	19.8
11f	M.b. medium	0	1	8	33	47	20	9	1,955	217.2
12b	M.b. medium	0	22	78	62	33	5	36	1,000	27.7
17e	B.g. medium	18	71	11	89	9	2	84	1,000	11.9
19c	M.b. dark	26	66	8	72	22	6	9	780	88.9
19d	M.b. dark	20	76	4	75	16	9	7	111	15.9

* d-s = deeply stained; w-s = well stained; p = pale.
† M.b. = methylene blue; B.g. = brilliant green.

in diagnosis depends upon proper staining and a suitable counterstain. Computing the general average regardless of intensity of counterstain (table 3, combined) the superiority ratio for restaining is for direct smears, 5.77 and for concentration films 16.01. Restaining gives superiority ratios in films prepared by concentration almost three times as great as in those films prepared by direct smear. This same trend was reported (1) in an experiment comparing lightly stained and deeply stained films resulting in ratios of 3.14 in direct smears and 8.39 in films prepared by dilution-flotation. This greater improvement in result found in concentration and dilution-flotation films by deep staining is probably

due to the inhibitory action of the chemicals used. This inhibitory action is strong in light staining but is overcome by deep staining.

Table 4 gives the records of the 8 most inferior preparations with superiority ratios for restaining of 10 or better. The chief cause of failure in the first 5 preparations was understaining and in the last 3 heavy counterstaining. In 11f the organisms were stained just at the border of visibility; on restaining there were about 50 per field. In film 19c the organisms were stained fairly well, but the intense application of methylene blue rendered them almost wholly invisible. Restaining showed about 5 organisms per field.

Such errors as occur in making stain penetration differentials when dark counterstains are used, undoubtedly favor the original film since pale organisms are much less likely to be seen than those deeply stained.

These 8 inferior preparations came from 7 different institutions, and the 20 most inferior preparations came from 11 different institutions. This suggests that inferior results may occur unrecognized in any laboratory, unless adequate control of staining is employed.

Since Cooper's method of staining has been strongly recommended for increasing stain penetration a summary of the results from these films is given. There are 4 series totalling 31 films stained by this method. The average differential is 52 — 44 — 4 compared with the general average (table 2) of 22.6 — 61.1 — 16.3. The average restain differential for this group is 83.9 — 14.7 — 1.4. While this method leads in stain penetration in this survey, it lags substantially behind the results obtained on restaining.

Certified stains gave average differentials of 21.1 — 59.7 — 19.2 compared with 20.1 — 60.6 — 19.3 for uncertified, indicating no advantage of the former over the latter.

DISCUSSION

It has long been known that an undetermined number of organisms are unstained or understained by our usual staining methods. Some years ago Cooper (3) reëmphasized the importance of this view, and offered a staining technique to correct the deficiency. By the addition of salt solution to the fuchsin solution he observed much improvement in stain penetration.

The writer, reporting (1) nine years' experience with controlled staining, advocated the method as a means for accepting or rejecting a film under investigation. It was shown that a high percentage of deeply stained organisms (70 per cent or better) indicated that few if any pale organisms could be found except in the deeper layers of thick films. On the other hand, where the percentage is low, the number of pale organisms is likely to be increased, many of which are just on the border of visibility and others are not stained at all.

Since all films studied in this survey were positive and offered little difficulty in giving a positive report, such deficienceis in technique as were observed become of much importance in case the organisms are rare or not present at all, assuming that the same technique would be employed. The group of original films, 44 in number giving less than 100 organisms in a ten-minute search, is of special importance in this relation.

The most important deficiencies noted are failure to secure proper stain penetration and the application of strong counterstains which mask the organisms, causing poor visibility. Our data do not permit separation of these two deficiencies, but the combined method of controlled staining followed by picric acid as counterstain gave average ratios of superiority in direct smears of 5.77 and in concentration films of 16.01.

A lesser deficiency observed was that these 44 films on the average were only .38 as thick as they could be compared with a thickness of .44 for all films. Optimum films would be nearly three times as thick, with a corresponding increase in organisms per field. While the advantage in diagnosis would not be doubled it would be appreciably increased as was shown elsewhere (2).

Still another deficiency of undetermined value should be pointed out, relative to the making of direct smears. In accordance with universal experience, those films streaked on the slide with the platinum loop showed many consecutive negative fields followed by one or more fields, with plenty of organisms. One film observed, 15*c*, gave a ten-minute count of 21 organisms, and in the eleventh minute a single field was found containing 76 organisms. Careful inspection of this film after the record was made gave no indication that one would select this favorable portion of the film in the first instance; it was found simply by chance. Assuming that these findings represent the average for the film, the superiority of proper distribution over poor distribution would be indicated by $\frac{21 + 76}{11} \div \frac{21}{10} = 4.2$.

SUMMARY AND CONCLUSIONS

Contemporary opinion concerning staining methods for *Mycobacterium tuberculosis* and results of a study of 137 stained films received from 21 institutions are presented.

Relative to understaining of preparations, 15 expressed belief that the particular method employed protected against understaining and 5 stated that no special method was employed.

As to placing a positive control on the slide with the unknown, 13 strongly opposed the method, 6 considered it unnecessary, 3 approved and one expressed an open mind.

Ten used certified stains exclusively, 8 considered them unnecessary and 3 used both certified and uncertified.

Of counterstains used, 13 preferred methylene blue .02 per cent to Loeffler's full strength; 4, brilliant green; 2, picric acid; one, fast green; and one, malachite green.

As to staining, 13 steamed their films with carbol fuchsin, ranging from three to twenty minutes; 4 used Cooper's method; and 4 employed the cold method, ranging from forty-five minutes to twenty-four hours.

A wide variation in stain penetration was observed in films from different institutions and in films from the same institution, indicating that a uniformly dependable result cannot be secured without a definite method of control.

Restaining the original films for fifteen minutes at 65°C. and counterstaining with picric acid gave an average of 7.34 times as many organisms in a ten-minute continuous search as were found in the original films, covering essentially the same area in both counts.

The greatest ratios of superiority for the restain were found in those films counterstained with strong solutions of methylene blue and brilliant green, which contained less than 100 organisms in a ten-minute search, and in those films in which the organisms were markedly understained.

Controlled staining and the use of pale tints in counterstaining are recommended as a correction for most of the defects observed in this survey.

The 20 most inferior films came from 11 different institutions, indicating that an unfavorable result may occur in any laboratory unless adequate control of staining is employed. These films on restaining gave superiority ratios of six-fold or greater with an average ratio of 24.1.

SUMARIO Y CONCLUSIONES

Esta reseña presenta la opinión actual acerca de los métodos de coloración del *Mycobacterium tuberculosis* y el resultado de un estudio de 137 películas teñidas recibidas de 21 instituciones.

Con respecto a la subcoloración de los ejemplares, de 15 instituciones manifestaron que la técnica dada utilizada resguardaba contra la subcoloración, y 5 afirmaron que no empleaban ninguna técnica especial.

En cuanto a la colocación de un testigo positivo en la película con la incognita, 13 mostraron decidida oposición al método, 6 lo consideraron innecesario, 3 lo aceptaron, y uno se mostró indeciso.

Diez empleaban exclusivamente colorantes certificados, 8 los consideraban innecesarios, y 3 utilizaban tanto los certificados como los otros.

De los contracolorantes utilizados, 13 prefieren el azul de metileno al 1/50 por ciento al Loeffler a concentración completa; 4, el verde brillante; 2, el ácido pícrico; uno, el verde resistente, y uno el verde de malaquita.

En cuanto a coloración, 15 trataban sus ejemplares con vapores de carbolfucsina durante un período que variaba de tres a veinte minutos; 4 utilizaban el método de Cooper y 4 utilizaban la técnica fría por espacios que variaban de cuarenta y cinco minutos a veinticuatro horas.

Se observó una amplia variación en la penetración de los colorantes en las películas procedentes de diferentes establecimientos y hasta en las del mismo establecimiento, indicando que no puede obtenerse siempre un resultado fidedigno si no hay un método preciso de fiscalización.

La recoloración de las películas primitivas por espacio de quince minutos a 65° C., y la contracoloración con ácido pícrico dió por término medio 7.34 veces más microbios en una pesquisa continua de diez minutos, que los que se descubrieron en las películas primitivas, abarcando más o menos la mismo zona en ambas numeraciones.

La recoloración reveló su mayor superioridad en las películas contracoloreadas con soluciones concentradas de azul de metileno y de verde brillante, que

contenían menos de 100 microbios y estudiadas por diez minutos, y en las que los microbios estaban claramente subteñidos.

Como remedio para la mayor parte de las deficiencias observadas en este estudio, recomiéndase la coloración fiscalizada y el empleo de tintes claros en la contracoloración.

Las 20 películas más inferiores procedían de 11 instituciones distintas, lo cual indica que en cualquier laboratorio pueden obtenerse resultados deficientes a menos que fiscalicen adecuadamente la coloración. Estas películas inferiores, al ser recoloreadas, acusaron coeficientes de superioridad de seis veces o más, con un promedio de 24.1.

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BOVINE TUBERCULOSIS[1,2]

Its Incidence in Bone, Joint and Cervical Lymph Node Lesions in Italy

PAUL F. DE GARA[3]

LITERATURE

The biological properties of the bovine type of the tubercle bacillus have been known for more than 40 years (Smith (1)). Its importance in human pathology has been the object of much discussion since the first cases of human tuberculosis caused by the bovine type were reported by Ravenel (2). Approximately 18,000 strains of tubercle bacilli isolated from human lesions have been identified throughout the world and approximately 10 per cent were of the bovine type (3). This type is of little importance in the pathogenesis of human pulmonary tuberculosis; the highest incidence (7 per cent) was reported in 1940 in cases studied in Northeast Scotland (4). This type of bacillus, however, has been isolated frequently from extrapulmonary lesions (bone and joints, cervical lymph nodes, skin, intestinal tract and genito-urinary and nervous system).

Elaborate statistics by various authors have shown that the incidence varies considerably in various age groups and in different countries. English (5) and Danish (6) workers have reported that human extrapulmonary lesions due to the bovine type are much more frequent in children under five years of age than in the age group between five and fifteen. The incidence in adults was found to be still lower. This can be explained by the fact that more infected raw milk, an important source for the infection, is consumed by the younger age groups.

The incidence of extrapulmonary lesions of this type also shows considerable regional variation. Table 1 was compiled from the latest available reports from the different countries of Europe and gives the percentage of bovine strains isolated from bone, joint and cervical lymph node lesions (5 to 14). The high incidence in Scotland, England, Denmark and Switzerland is probably due at least in part to the large amount of milk and milk products consumed. In Poland and Greece, on the other hand, poor economic conditions may account for the fact that fewer dairy products are used and, therefore, fewer infections of bovine origin are likely to occur. Similar conditions also prevail in China (15).

In the United States, 1,362 strains of tubercle bacilli have been classified; 160 of these (11.7 per cent) were of the bovine type (3). Forty-four bovine strains were isolated from 199 patients with bone and joint lesions (22.1 per cent) (16 to 19) and 49 from 132 patients with cervical lymph node lesions (37.1 per cent) (16 to 22).

The great number of bovine strains isolated by Chang (19) is partly responsible for the apparent relatively high percentage of extrapulmonary tuberculosis due to the bovine type in this country. However, Chang's methods and criteria for the type determination of tubercle bacilli cannot be considered satisfactory. Furthermore, in the United States the actual percentage of cases due to the bovine type is certainly lower because many workers did not report their results if they did not find any bovine tubercle bacilli.[4]

[1] Aided by a grant from the C. Forlanini-Foundation, Milan, Italy.

[2] These investigations were carried out, from 1934 to 1939, at the Hygienic Institute of the University of Milan, Italy, in part collaboration with Dr. G. Sollazzo.

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[4] Max Pinner: Personal communication, 1941.

It is well known that tubercle bacilli may enter the body by way of the gastro-intestinal tract, affecting the cervical and mesenteric lymph nodes. Extrapulmonary lesions in children, due to the ingestion of bovine tubercle bacilli with infected milk, are an example of this mechanism of infection. Therefore, special attention was given to intestinal tuberculous lesions, as observed at autopsy. Primary intestinal tuberculosis is uncommon in this country. Ophüls (23) found obsolescent lesions of the mesenteric lymph nodes in less than 6 per cent of autopsies performed in San Francisco. Opie (24) in a series of St. Louis cases found no lesions in the mesenteric lymph nodes in 93 autopsies

TABLE 1

Incidence of bovine tuberculosis in various European countries in bone, joint and cervical lymph node lesions

COUNTRY	BONE AND JOINT LESIONS		CERVICAL LYMPH NODE LESIONS	
	Total number examined	Percentage of bovine bacilli	Total number examined	Percentage of bovine bacilli
Scotland	218	29.8	93	51.6
England	553	19.5	126	50.0
Denmark	567	18.5	251	49.0
Switzerland	59	10.1	8	37.5
Germany	87	4.6	94	22.3
Spain	53	3.7	18	16.6
Hungary	—	—	64	6.2
Greece	47	0	70	0
Poland	13	0	8	0

TABLE 2

Incidence of bovine tuberculosis in Italy

VARIETY OF TUBERCULOSIS	TOTAL NUMBER EXAMINED	BOVINE TYPE	
		Number	Percentage
Bone and joint	8	1 (?)	12.5 (?)
Cervical lymph node	27	1	3.7
Other extrapulmonary	217	14	6.4
Pulmonary	657	20	3.4
Total	909	36	3.9

on children and in 50 autopsies on adults. The same author, however, reported caseous or calcified mesenteric lesions in 18 of 66 (27 per cent) of the autopsies performed during the first World War on young British soldiers (25, 26).

In Italy, according to previous reports (27 to 40), 36 of 909 (3.9 per cent) strains of tubercle bacilli, isolated from human lesions, were found to be of the bovine type (table 2).

More than 500 specimens from tuberculous pulmonary lesions were examined (32, 39), but only a few were obtained from cases with bone and joint lesions. Of the 27 cases with cervical lymph node lesions 26 were reported in 1912 (27), and only one additional case has been added since then (29). In the mixed group of other extrapulmonary lesions the specimens were obtained from the urogenital tract, the meninges, the skin, etc. In this group total numbers varying from one to 60 specimens were examined.

The object in undertaking the present investigation was to study on a larger scale the incidence in Italy of bovine tubercle bacilli in bone, joint and cervical lymph node lesions.

A preliminary report of the first 63 cases studied was presented at the Sixth Italian Congress of Microbiology in Milan, in 1937 (41). These cases are incorporated in the present report.

MATERIALS AND METHODS

The specimens were obtained, with the collaboration of the resident physicians, from the bone, joint and cervical lymph node lesions of tuberculous patients in various sanatoria in Milan and other localities in Northern Italy (Venice, Riviera). The material was procured by aseptical puncture of closed and untreated lesions and forwarded immediately to the laboratory at Milan.

Three to 5 cc. of the tuberculous material were mixed in a sterile 50 cc. tube with an equal amount of an 8 per cent solution of sodium hydroxide. After twenty minutes, 40 cc. of distilled water were added and the mixture centrifugalized for thirty minutes at 3,000 r.p.m. The supernatant fluid was discarded and the sediment neutralized with diluted sulfuric acid. One-half cc. portions of the sediment were transferred into large tubes containing Petragnani's malachite-green-egg medium with 3 per cent glycerin, or into tubes containing Petragnani's medium without glycerin, but with the addition of 1 per cent virgin wax (42). The human type grows readily on both media in rough, dry, pigmented colonies; the bovine bacilli frequently grow only in the presence of virgin wax and without glycerin in humid, smooth, nonpigmented, whitish colonies. The tubes were closed with sterilized cork stoppers and incubated at 37°C. in oblique position in order to spread the sediment over a larger surface of the medium. Growth usually occurred within three weeks, and sometimes as early as ten day. The cultures were examined macroscopically to determine gross appearance, pigmentation and growth on the different media, and microscopically in Ziehl-Neelsen stained preparations.

The growth of 30 strains was so typical as to permit their immediate classification as human types; the remaining 165 strains were injected into rabbits and guinea pigs for final type determination. The bacillary mass was removed from the culture medium by means of a platinum spatula and placed on a piece of sterile filter paper to remove excess moisture. It was then transferred to a tared piece of sterile platinum foil, weighed and emulsified in an agate mortar with the addition of a sufficient amount of 0.9 per cent sodium chloride solution to make a concentration of 0.01 mg. of tubercle bacilli per cc.

Healthy male rabbits, weighing 2,000 to 2,500 g. were given intravenous injections of 1 cc. (0.01 mg.) of the suspension made from a three to four weeks old culture of the first isolation. The guinea pigs were given subcutaneous injections of 0.5 cc. (10 mg.) of culture into the right inguinal region. Most of the animals died within eighteen to ninety days after the injections; those which survived were killed between the nintieth and one hundred and forty-seventh day. A complete autopsy was performed on each animal, and material from visible tuberculous lesions was again cultured on Petragnani's media.

The strains which presented a typical humid, smooth, whitish growth on the media, especially that containing virgin wax, and which killed the rabbits within three to ten weeks after the intravenous injection with a generalized tuberculosis were classified as bovine tubercle bacilli. A few bovine strains presented typical

growth on the media, but were of low virulence for rabbits and guinea pigs. The human strains showed typical dry, rough, pigmented growth. A few behaved atypical when injected into rabbits; the other strains produced only moderate, localized lesions, usually confined to the lungs. Guinea pigs presented a generalized tuberculosis.

RESULTS

The specimens were obtained from 174 tuberculous lesions of the bones and joints and from 21 cervical lymph node lesions. Table 3 shows the types of tubercle bacilli isolated from these cases.

In addition, 13 specimens were obtained from patients suffering from various other extrapulmonary lesions (renal, meningeal, etc.). The human type of tubercle bacillus was isolated from these 13 cases.

Including our results with those of other workers, a total of 1,117 strains of tubercle bacilli has been classified in Italy (table 2); of these strains 54 (4.8 per cent) were found to be of the bovine type.

TABLE 3

Types of tubercle bacilli found in bone, joint and cervical lymph node lesions

VARIETY OF TUBERCULOSIS	TOTAL NUMBER EXAMINED	HUMAN TYPE		BOVINE TYPE	
		Number	Percentage	Number	Percentage
Bone and joint	174	161	92.6	13	7.4
Cervical lymph node	21	16	76.2	5	23.8
Total	195	177	90.8	18	9.2

Human type: The growth of all the 177 human strains isolated was typical on both the glycerin and virgin wax media: the colonies were dry, rough and showed a yellow pigmentation.

As already stated, the growth of 30 human strains was so typical as to permit their immediate classification as such and, therefore, no animals were injected with these strains. Rabbits and guinea pigs were infected with the remaining 147 strains. All were highly pathogenic for guinea pigs and caused a generalized tuberculous. In rabbits infected with 143 of the strains and killed after three months either no lesions could be detected or the tuberculosis found was negligible, consisting of only a few, small, localized foci, usually in the lungs and occasionally in the spleen or kidneys. The remaining 4 strains, which had been obtained from bone and joint lesions, grew typically in dry, rough colonies, but their virulence for rabbits was increased. Three of the strains killed the rabbits after seventy-three, eighty-five and ninety days, respectively. At autopsy tuberculous lesions were found in the lungs of all 3 rabbits, small foci in the spleen in two instances and in the kidney in one instance. The rabbit injected with the fourth strain was killed after one hundred days; moderate pulmonary lesions and enlargement of the inguinal lymph nodes with partial caseation were

found. However, the lesions in the 4 rabbits were never as extensive as those observed in the animals injected with the bovine bacilli.

Bovine type: The cultural properties and the pathogenicity of the bovine strains are given in table 4.

All 18 bovine strains showed a typical growth (humid, smooth, whitish, nonpigmented colonies). Eleven strains grew only on the wax medium, one strain grew only on glycerin medium and the wax medium of one strain was contaminated.

TABLE 4

Cultural properties and pathogenicity for rabbits and guinea pigs of the bovine tubercle bacilli isolated from bone, joint and cervical lymph node lesions

NUMBER	LESION	GROWTH ON PETRAGNINI'S MEDIUM CONTAINING		DAY OF DEATH	PATHOGENICITY	
		Glycerin	Virgin-wax		Rabbits—organ lesions	Guinea pigs—organ lesions
1	B-J	0	+	18	Lungs	
2	B-J	+	+	23	Generalized	Generalized
3	B-J	+	+	23	Generalized	
4	B-J	+	+	33	Generalized	
5	C-N	0	+	38	Generalized	Generalized
6	C-N	+	Contaminated	39	Generalized	Generalized
7	B-J	0	+	44	Generalized	
8	B-J	+	+	44	Generalized	Generalized
9	B-J	+	+	44	Generalized	Generalized
10	B-J	±	+	45	Generalized	
11	C-N	+	+	56	Lungs	Lymph nodes
12	B-J	0	+	63	Generalized	
13	B-J	+	+	64	Lungs, liver, spleen	Lymph nodes
14	B-J	+	+	72	Generalized	
15	C-N	+	+	75	Generalized	Generalized
16	B-J	+	+	110*	Lungs, liver	Lymph nodes
17	C-N	+	+	133	Lungs, kidneys	Lymph nodes
18	B-J	+	0	136*	Lungs, kidneys	Lymph nodes

Key: B-J = bone and joint, C-N = cervical node, * = killed, 0 = no growth, ± = slight growth, + = growth.

Rabbits were injected intravenously with 18 bovine strains. Sixteen of the animals died from eighteen to one hundred thirty-three days after the infection (average 50.8 days); the 2 remaining rabbits, infected with strains 16 and 18, respectively, were killed on the one hundred tenth day (strain 16), and on the one hundred thirty-sixth day (strain 18). Twelve rabbits presented a generalized tuberculosis. Two rabbits showed extensive tuberculous lesions of the lungs and kidneys, one of the lungs and liver, and one of the lungs, liver and spleen. The 2 remaining rabbits presented lesions of the lungs only. One of these died only eighteen days after the injection; this may explain why the infection was not yet detectable in other organs. The other was injected with strain 11 which was apparently of low virulence for both guinea pigs and rabbits.

Injections of the bovine strains into guinea pigs gave the following results (table 4):

Animals injected with 6 of the strains, which were also highly virulent for rabbits, presented a generalized tuberculosis. Five strains of an apparently low virulence for both rabbits and guinea pigs caused caseous tuberculous lesions of the inguinal lymph nodes, and in 3 instances, of the iliac lymph nodes as well. The guinea pigs injected with the remaining 7 strains died within the first six days of an intercurrent disease.

AGE DISTRIBUTION OF THE PATIENTS

The age distribution of the patients affected with bone, joint and cervical lymph node lesions from whom the specimens containing tubercle bacilli were obtained is given in table 5.

The total number of cases examined in the younger age groups is too small to be of statistical significance.

TABLE 5

Age distribution of patients in relation to type of tubercle bacilli isolated from bone, joint and cervical lymph node lesions

AGE	TOTAL NUMBER EXAMINED	BOVINE TYPE	
		Number	Percentage
Up to 5 years	5	2	40.0
5 to 15 years	36	6	16.6
Over 15 years	154	10	6.4

CONSUMPTION OF INFECTED MILK

In Italy most babies receive maternal nursing during the first twelve months. In our series, 2 (11 per cent) of the patients with bovine bacilli and 27 (15 per cent) of those with human bacilli in their extrapulmonary lesions had been fed on formulae of cow's milk, beginning shortly after birth. The data obtainable from most of the patients concerning consumption of raw milk in later life were vague, and no conclusions as to the importance of the consumption of infected milk in the pathogenesis of their tuberculosis could be drawn.

CONTACT WITH CATTLE

Five of the 18 patients (27.5 per cent) affected by the bovine type of tuberculosis had been in the past in almost constant contact with cattle. The patients, whose ages were three, four, ten, eighteen and twenty-two years, respectively, were born and raised on farms in Northern Italy. Either through the consumption and handling of infected milk, or because of generally bad hygienic conditions, infection with bovine tubercle bacilli was a major possibility in these cases. Of those affected by the human type, 26 of 177 (14.6 per cent) were born or lived on farms or, as veterinarians, had had repeated contacts with cattle.

DISCUSSION

In 1937 Petragnani (43) reported that the incidence of human tuberculosis caused by the bovine type of tubercle bacillus could be considered extremely rare. This statement was based upon examinations of 557 patients in Italy which had yielded only 12 bovine strains (2.1 per cent).

In our series, unfortunately, only a comparatively small number of cases could be examined in the younger age groups. The results obtained are, therefore, not of statistical value. A considerably higher incidence of the bovine type was observed in children than in adults: 40 per cent in the group below five years of age; 16.6 per cent in the group from five to fifteen years; and 6.4 per cent in those over fifteen years of age. This age relationship is in agreement with observations made by Griffith (5) and others.

The results of the present investigations show that in Italy extrapulmonary tuberculosis caused by the bovine tubercle bacillus is not extremely rare, and also that the percentage of cases in all age groups is considerably lower than that reported from other European countries (Great Britain, Denmark, etc.).

Infected raw milk from tuberculous cows has always been considered an important aetiological factor in infections caused by the bovine tubercle bacillus. In Italy, 37 of 544 samples of market milk (6.8 per cent) were found to be contaminated (3). Pasteurization of all milk used for human consumption is well known to be an efficient way to control bovine tuberculosis in man; this method is used in Italy only in larger communities. The danger of using nonpasteurized infected milk is greatly reduced by the household custom of boiling milk to prevent it from going sour. This unwittingly hygienic procedure prevents many infections among the population of Northern Italy where bovine tuberculosis is still wide-spread. The most radical way of controlling bovine tuberculosis in man by eradication of the disease in its natural host meets with economic difficulties and, therefore, has not yet been applied in Italy on a larger scale. In our series the data obtained were insufficient to establish an aetiological relationship between the prolonged consumption of infected raw milk and infection with the bovine type of tuberculosis.

Cosco (44) reported that not only the milk of infected cows, but in 7 of 9 instances, the faeces, and in 2 of 9 instances, the saliva, may also contain large amounts of tubercle bacilli. This may explain the mode of infection in a certain number of our cases who had had prolonged or repeated contact with cattle.

Tuberculosis of swine may be caused not only by the avian, but also by the bovine tubercle bacillus (45). No investigations on this type of infection have been published in Italy but some of our cases may have contracted their infection by the consumption of infected pork.

Finally, the bovine tubercle bacillus may be transmitted by direct contact from man to man. This may be considered as a potential source of infection in Italy where the incidence of the bovine type of tuberculosis in humans is approximately 5 per cent although according to Opie (46): " . . . There is no convincing evidence that tuberculosis produced by the bovine bacillus is transmitted from one human being to another."

SUMMARY

In 195 cases of extrapulmonary tuberculosis, examined from 1934 to 1939 in Northern Italy, the bovine type of tubercle bacilli was found in 18, or 9.2 per cent.

Of these cases, 174 had tuberculous bone and joint lesions, 13 of which (7.4 per cent) were caused by bacilli of the bovine type. The remaining 21 cases had cervical lymph node lesions; 5 of these (23.8 per cent) were due to the bovine type.

Bovine tuberculosis was observed in 40 per cent of the children below five years of age, in 16.6 per cent of those between the ages of five and fifteen years, and in 6.4 per cent of the persons older than fifteen years.

The importance of infected raw milk or of prolonged contact with infected cattle in the aetiology of infection with bovine tubercle bacilli is discussed.

SUMARIO

En 195 casos de tuberculosis extrapulmonar estudiados de 1934 a 1939 en el Norte de Italia, se encontró el tipo bovino del bacilo tuberculoso en 18 (9.2 por ciento).

De estos casos, 174 tenían lesiones osteoarticulares, 13 de las cuales (7.4 por ciento) habían sido ocasionadas por bacilos de tipo bovino. En los otros 21 había lesiones de los ganglios cervicales, debiéndose en 5 de ellos (23.8 por ciento) al tipo bovino.

Se observó tuberculosis bovina en 40 por ciento de los niños de menos de 5 años, en 16.6 por ciento de los de 5 a 15 años, y en 6.4 por ciento de las personas mayores de 15 años.

Discútese la importancia que poseen la leche cruda infectada o el prolongado contacto con ganado vacuno infectado en la etiología de la infección producida por bacilos bovinos.

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LABORATORY AND CLINICAL NOTES

BOVINE TUBERCLE BACILLI IN SPUTUM[1, 2]

MARGARET BEATTIE AND ROBERT NICEWONGER

Many workers have studied the types of *M. tuberculosis* isolated from sputum specimens. A compilation of their results has been made from a study of nearly one hundred references. A summary of these findings is presented in table 1, in which the countries are indicated from which the data were obtained. The consensus derived from these studies is that pulmonary disease caused by bovine strains of the tubercle bacillus is rare, but that such infection may occur in areas where raw milk from tuberculous cows is consumed.

Since bovine strains have been isolated from sputa in various European countries where tuberculosis is prevalent in milking herds, and since many of the cows in the milking herds in California were and some still are tuberculous, it was felt that it would be interesting to study the types of tubercle bacilli isolated from sputa from persons in various sections of the state. The decision to undertake this problem of type differentiation was made after approximately 200 strains of tubercle bacilli had been isolated from sputa as a part of another study. Most of the strains previously isolated had been discarded. However, 82 strains isolated from specimens obtained from the Oakland City Health Department Laboratory and the Bacteriological Laboratory of the State Department of Public Health were available and were tested for type. It was decided that additional specimens should be collected from widely separated areas throughout the state. Beginning in January, 1938, specimens were received from various county institutions. Approximately 300 strains were isolated from sputa from patients in hospitals and tuberculosis sanatoria located in counties scattered throughout the state. It was felt that strains of tubercle bacilli isolated from the sputa of patients in these institutions would constitute an adequate and representative sample.

Technical procedures: All smear preparations were fixed by heat and stained with cold concentrated carbol-fuchsin and Gabbett's solution. During the first month of this study, the sputum specimens were treated by Holmes' (1) modification of Jensen's method. It was found that many of the cultures were overgrown by molds so the method recommended by McNabb (2) was adopted. From September, 1936 until August, 1938, Petragnani's (3) medium was used. After August, 1938, Saenz and Costil's (4) modification of Petragnani's medium (the addition of asparagin in place of peptone) was adopted. It was noted that growth appeared much earlier on this medium. The medium was placed in rectangular, clear, 2-ounce glass bottles fitted with screw caps.

Method of typing: The amount of growth of all strains was noted after six weeks' incubation on medium which had been seeded directly from the concentrated sputum. Some of the growth of these primary cultures was triturated

[1] From the Department of Hygiene, University of California, Berkeley, California.

[2] Aided by a grant from the Research Board of the University of California.

in salt solution to insure even distribution of the organisms and the suspension seeded onto four bottles of Petragnani's medium, two containing glycerine and two without glycerine. Rough standardization of this suspension was made by comparison with a nephelometer tube. These secondary cultures were observed weekly for six weeks. At the end of this time the cultures were classified as eugonic or dysgonic.

A suspension containing 0.1 mg. of a culture of each dysgonic and atypical eugonic strain was injected intravenously into a rabbit. The viability of the inoculum was determined by the inoculation of the suspensions onto media or into guinea pigs.

TABLE 1

Incidence of bovine tubercle bacilli in sputa

COUNTRY	TOTAL STRAINS	HUMAN STRAINS		BOVINE STRAINS		UNCLASSIFIED STRAINS	
		Number	Per cent	Number	Per cent	Number	Per cent
England	2,630	2,577	97.0	52	2.0	1	less than 0.1
Scotland	1,934	1,831	94.7	103	5.3	0	0
Ireland	320	320	100.0	0	0	0	0
Canada	48	47	98.8	1	2.1	0	0
Australia	27	27	100.0	0	0	0	0
Trinidad	40	40	100.0	0	0	0	0
Germany	561	539	96.1	19	3.4	3	0.5
Denmark	1,975	1,854	93.9	121	6.1	0	0
U. S. A.	348	348	100.0	0	0	0	0
France	266	266	100.0	0	0	0	0
	7 839			296	3.64	4	

RESULTS OF STUDY

Strains of *M. tuberculosis* were isolated from 366 persons. The growth characteristics of each strain were observed. Of the 366 strains studied, 19 presented a dysgonic type of growth. All these dysgonic strains, as well as 14 strains which exhibited an atypical eugonic type of growth, were injected intravenously into rabbits.

In only 15 of the 33 rabbits inoculated were any pulmonary lesions observed. The involvement was very slight in these 15 animals and in marked contrast to the extensive pulmonary lesions of control animals inoculated with known bovine strains. Macroscopical visceral lesions were demonstrated in 4 rabbits. In one rabbit three small tubercles were present in the liver and in 3 other animals minute lesions in the kidneys were observed. The rabbits inoculated with known bovine strains had large tubercles in the spleen, liver and kidneys no matter how small the dose.

SUMMARY

Three hundred and sixty-six strains of *M. tuberculosis* were isolated from the sputum of persons in sanatoria and hospitals in various counties in California. These were classified for type by growth on culture media. Those strains which

appeared to be dysgonic and those not typically eugonic were tested by rabbit inoculation. Of the 366 strains so studied none was identified as the bovine type of *M. tuberculosis*.

SUMARIO

Del esputo de las personas presentes en los sanatorios y hospitales de vavrios condados de California se aislaron 366 cepas del *M. tuberculosis*, que se clasificaron en cuanto a tipos cultivándolas en medios apropiados. Las cepas que parecían ser disgónicas y no típicamente eugónicas fueron comprobadas mediante la inoculación en el conejo, y de las 366 así estudiadas ninguna fué identificada con el tipo bovino del *M. tuberculosis*.

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STEAM HEATING SYSTEM AS A SOURCE OF SUCTION[1]

For Intracavitary Aspiration

JOHN V. THOMPSON

Various means have been devised to produce suction for the transthoracic aspiration of tuberculous cavities. The following frequently available source of vacuum may be adapted for this purpose.

Steam radiators drained by a vacuum which is produced by a central pump in the heating plant are used in many buildings. A ready source of suction, therefore, is available in every room in which a radiator is present where this type of heating system is installed. Technical aspects regarding maintenance of the vacuum must necessarily be determined somewhat by the local conditions.

As illustrated in the accompanying diagram, in order to tap this source of suction, a T-pipe fitting (E) or other applicable steam fitting unit is connected in the vacuum line distal to the steam trap (W) of the radiator.

The following devices of everyday usage have been found satisfactory in regulating the suction in the local system. A half inch (or smaller size) gas check-valve (V), permitting only unidirectional flow, is inserted as a safety factor. A quarter inch reducing-petcock (P) is incorporated to adjust the vacuum in the system to approximately the desired negative pressure and may be used to turn off or on the suction. A hard red rubber tubing (D) connects to a common type of water-valve pressure control (R).

This control consists of a glass cylinder or bottle of about 30 cm. in height with a three-hole rubber stopper through which pass two short sections of glass tubing. One connects to (D) and the other to a rubber tubing (H) leading to a simple water manometer (M). A third glass tubing (A) is open to the atmosphere and extends to the bottom of the cylinder below a water level. A centimetre scale is placed behind the cylinder.

The water manometer consisting of a U-shaped tubing and containing a colored aqueous solution is connected into the system by a glass T tube (T) attached to rubber tubings (H) and (I). The manometer should have long columns to prevent the loss of fluid as it is an advantage to have it continuously in operation and measuring the pressures in the system at all times. Graduations in centimetres to 75 or more on each side of zero are necessary if intracavitary pressures are to be observed under various conditions. (On the scale 1.0 cm. is actually measured off as 0.5 cm. inasmuch as one column rises 0.5 cm. above and the other column drops 0.5 cm. below zero for every 1.0 cm. of difference between the fluid levels of the two columns.)

A bottle (S) with a two-hole stopper through which pass two short lengths of glass tubing—one longer than the other and connected to a rubber tubing (B) leading to the object to be aspirated with the other connected by tubing (I) to the manometer—acts as a trap for aspirated material.

Another small cylinder (dotted in diagram) with a two-hole stopper through

[1] From the Sunnyside Sanatorium, Indianapolis, Indiana.

which pass two glass tubings—one extending slightly below a fluid level and connected to the trap with the short one attached to the manometer by dividing tubing (I)—will act as a rate of flow indicator.

The frame consists of shellacked pine with the devices attached by sheet metal strips and all parts are bolted so that they are detachable for boiling. An aqueous antiseptic solution may be used instead of water in the controls with some value.

In operation, the check-valve prevents any reversal of flow into the attached line if an accident should occur in the vacuum line of the heating system. The petcock is turned on just enough so that air bubbles very slowly through the liquid in the pressure control.

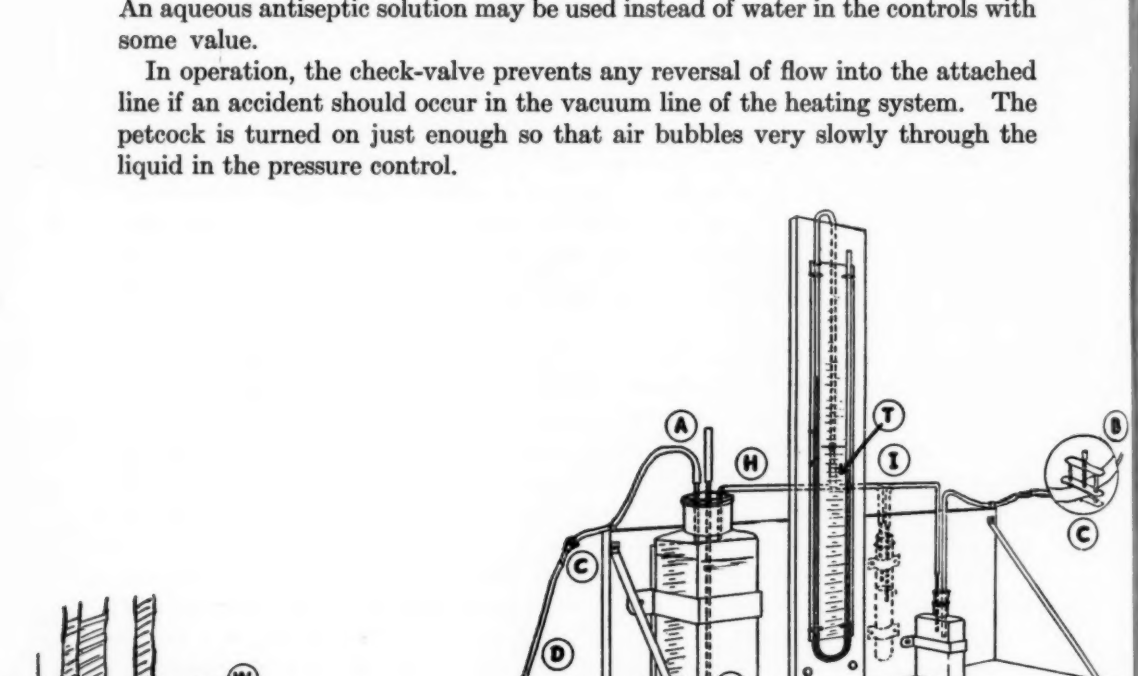


FIG. 1

Within reasonable limits, the water valve control tends constantly to maintain the desired degree of subatmospheric pressure. The water level in the cylinder is adjusted so that the height of the column of water, measured in centimetres, is the same figure as the desired degree of suction in terms of centimetres of water. If by accident a degree of suction is brought about within the local system which is greater than the height of the water column in the cylinder, atmospheric air rushes in through tube (A) to satisfy the pressure difference between that desired as determined by the height of the water level and that existing in the system. A marked rapid bubbling in the cylinder indicates this situation. If by the straining of a patient undergoing intracavitary aspiration or for other reasons a pressure greater than the height of tube (A) is brought about, fluid and then air will escape through the tube tending to reduce the pressure and to prevent trauma of the cavity.

During intracavitary aspiration the average reading of the oscillations on the manometer, which may vary with the respiration and position of the patient, should correspond to the height of the fluid level in the pressure control when the petcock is properly adjusted. The oscillations or non-oscillation also vary with the mechanical conditions present within the cavity, bronchus or catheter. Tests for intracavitary and intrabronchial conditions involving the use of a manometer may be made by clamping tubing (H) or disconnecting it and opening it to the atmosphere as desired or by the insertion of a Y-tube with the necessary pinch-clamps.

With the degree of suction fairly constant, the bubbling in the rate of flow indicator will vary with the respiratory cycles, broncho-cavitary state, the patency of the catheter or its connections during intracavitary aspiration and together with the manometer readings are frequently suggestive of the mechanical conditions present. Again the degree of suction may be adjusted to the existing conditions.

Patients undergoing treatment can be instructed as to the mechanics involved and the conditions desired. When the apparatus is placed at the bedside (somewhat lower than the body to facilitate drainage), the patients can be taught to make fine adjustments and to turn off the suction if necessary by means of screw-clamps (C).

The regulating devices are not innovations but are merely described as a means of adapting a frequently available source of vacuum in a steam heating system for suction, by use of which the pressure and rate of flow can be estimated and controlled. The entire set-up is inexpensive, easily constructed, not particularly subject to wear and tear, noiseless, convenient and requires little attention, except for occasional adjustments or periodic cleansing.

This method of suction has been satisfactory in the treatment of cavities by transthoracic aspiration during the past year in a relatively small number of cases. Its possible value is suggested for other purposes where controlled suction and maintenance of a specified subatmospheric pressure, particularly over a relatively long period, might be of benefit.

SUMMARY

The vacuum utilized to drain steam radiators may be adapted for suction in clinical work, particularly in the transthoracic aspiration of tuberculous cavities. The common inexpensive devices which may be used to tap and control the vacuum are described together with their operation.

SUMARIO

El vacío utilizado para limpiar los caloríferos de vapor puede ser adaptado para la succión en la clínica, y en particular en la aspiración transtorácica de las cavernas tuberculosas. Descríbense aquí dispositivos poco costosos y corrientes que pueden utilizarse para perforar y comprobar el vacío, junto con el funcionamiento de los mismos.

The author wishes to acknowledge the aid rendered by Dr. Edward B. Boyer and the other members of the medical staff of Sunnyside Sanatorium in the clinical adaption of the method.

AMERICAN TRUDEAU SOCIETY

Wisconsin Trudeau Society

The mid-winter session of the Wisconsin Trudeau Society was held at Muirdale Sanatorium, Wauwatosa, Wisconsin, on Saturday, January 17, 1942, between 2 and 9 p.m. About 70 physicians attended.

PROGRAM

Tuberculosis of the Genito-Urinary Tract in Its Relation to Collapse Therapy was discussed by Dr. James King of Milwaukee. The speaker postulated:

1: Tubercle bacilli appear in the urine only following kidney damage.

2: Genito-urinary tuberculosis in its early stage is usually haematogenous and most frequently bilateral.

3: It is possible for early tuberculous lesions in the kidneys to heal as elsewhere.

He pointed out that it was possible for tuberculosis to exist in a kidney despite negative laboratory tests.

Experimental and Clinical Pelvic Tuberculosis was presented by Dr. Ralph Campbell of Madison. The experimental animal used was the dog. Slides were shown depicting the uterus and tubes *in situ* following various laparotomies. Thickened tuberculous tubes apparently responded very nicely to deep X-ray therapy, with regression of the lesions and ultimate fibrosis. The speaker emphasized the possible relationship between the induction of menopause and regression of the lesions, stating that with menstruation we often see flaring up of tuberculous lesions.

Bronchospirometry presented by Dr. Wm. Coffey, Jr., and discussed by Dr. John Steele, both of Milwaukee, emphasized the fact that this procedure is relatively simple and should be used more often before deciding upon surgical procedures in patients with bilateral tuberculosis and with low vital capacity, to test the capacity of the better lung.

The symposium on *Miniature X-ray Films* by Drs. L. R. Cole and H. M. Coon of Madison, and Dr. E. R. Daniels of Milwaukee, was based on a study of 500 University of Wisconsin students who reacted to the tuberculin test. The significant point in this discussion was the fact that 35 mm. films, and 14 x 17 films agreed as far as the impression of significant secondary tuberculosis is concerned.

Dr. D. D. Feld of Milwaukee reviewed several case histories and films of *blastomycosis*. The majority of patients had both local and systemic manifestations of blastomycotic infection. He feels this disease is rarely transmitted from man to man, seldom is it connected with occupation, but it is more wide-

spread than formerly thought, and should be kept in mind in sputum and gastric contents in which tubercle bacilli cannot be demonstrated.

At the business meeting, the following officers presented by Dr. John K. Shumate, Chairman of the Nominating Committee, were unanimously elected:

Dr. Geo. Owen, Oshkosh, President
Dr. E. R. Daniels, Milwaukee, Vice-President
Dr. John Steele, Milwaukee, Secretary-Treasurer

Following the election of officers the Treasurer's report was made, and the next meeting of the Society announced. Plans are in progress to have a joint meeting of the Wisconsin and Michigan Trudeau Societies at the Four Seasons Club, Pembine, Wisconsin (Marinette County) on June 5 and 6, 1942.

The evening program included two excellent presentations. The first, on *Results of Certain Chemotherapeutic Agents in Experimental Tuberculosis* by Dr. W. N. Feldman of Rochester, Minnesota, demonstrated that promine acts as a deterrent agent in guinea pigs. Tuberculous lesions in the treated group became regressive instead of progressive in character as happened in the untreated control group. Fifty-two per cent of the animals treated with promine showed no evidence of tuberculosis in the spleen, kidneys or lungs on autopsy after 192 days, but all untreated animals died.

The second paper of the evening was by Dr. L. L. Collins of Ottawa, Illinois, on *The Advantage of Tuberculin Testing Surveys over the X-raying of Entire Groups without First Tuberculin Testing.* It showed particularly the need for both tuberculin testing and X-raying in apparently healthy individuals. Many films were used to illustrate the value of the skin test in ruling out tuberculosis when apparently typical shadows of this disease were seen on X-ray films. The speaker also stressed the value of the educational program in connection with mass tuberculin testing and felt that the practicing physicians should do the testing.

MEDICAL LITERATURE COPYING SERVICE

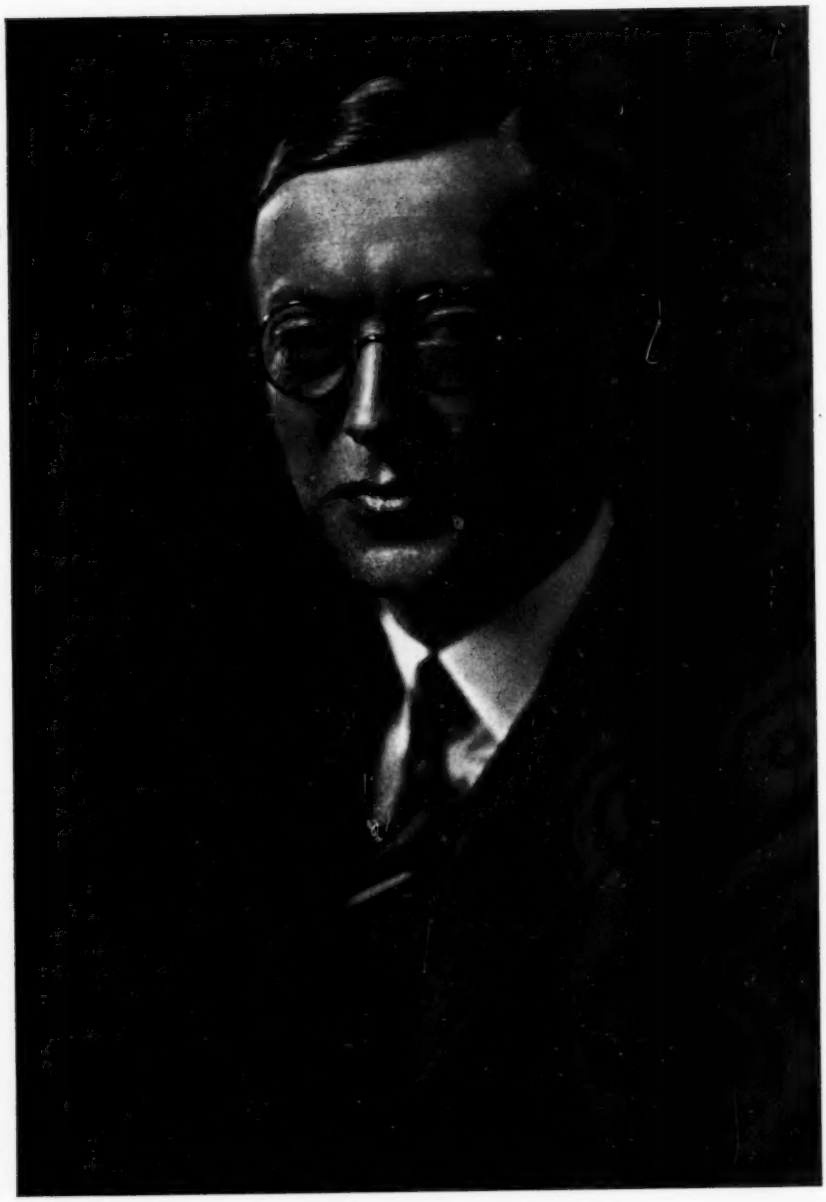
Microfilm copies of the papers referred to in the *Current List of Medical Literature* (published by the Friends of the Army Medical Library) may be obtained from Medicofilm Service of the Army Medical Library at twenty-five cents for each complete article, not exceeding 25 pages in length, and ten cents for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address: Medicofilm Service, Army Medical Library, Washington, D. C.

NOTICE

Dr. C. E. Turner, Head of the Department of Public Health of the Massachusetts Institute of Technology, makes the following announcement:

The Department of Public Health at the Massachusetts Institute of Technology, Cambridge, Massachusetts, is offering an accelerated program of public health training beginning June 8, 1942 and allowing for the completion of a Master's degree on February 6, 1943. These training programs are organized for public health engineers, health educators and public health laboratorians, as well as for administrators. Special summer courses are also being offered.

ALLEN KRAUSE with his prodigiously fertile mind has sown so many—named and unnamed—seeds that no one working in the field of tuberculosis does not owe him a debt of gratitude. But gratitude can but rarely be repaid to the creditor. It cannot be paid with printed words. This must be done—and is being done—in living action, by continuing the good work from which Allen Krause was so prematurely taken. Yet, gratitude, admiration, friendship, respect and devotion long for tangible manifestation. And so it is altogether an appropriate expression of our love and respect that the AMERICAN REVIEW OF TUBERCULOSIS, itself a monument to his work, should publish this issue dedicated to the memory of Allen Krause. Friends, coworkers, associates and former pupils have here coöperated. The Editorial Board and the authors are aware that this cannot be a *measure* of the echo that Allen Krause has aroused in his contemporaries—it is but a symbol of it.



Allen Kramer Krause
1881 - 1941

ALLEN KRAMER KRAUSE

A Brief Biographical Story

HENRY STUART WILLIS[1]

Once a man laid open his dream to his friend. As he did so, he engraved his medical credo and ambition in bold lines. His thought was threefold—namely: to push back the frontiers of our ignorance of tuberculosis; to arouse his fellow physicians to the importance of a fuller knowledge of tuberculosis; to give his fellow lay citizens information of value about this disease.

These were the points of the dream and plan.

1: To study: the why and how of the body's responses to the tubercle bacillus—why lazy first infection and rapid, abortive reinfection—why predominantly in lungs and why different in adults and children—why tubercle formation, etc. etc. etc.
2: To emphasize that other factors than the bacillus are important in the development of the disease tuberculosis.
3: To inspire, guide and direct through students and through publications.
4: To emphasize the value of the classics and, by critical translation and republication, give them their proper place in the history and literature of tuberculosis.
5: To point out medical achievements of our own countrymen.
6: To encourage sanatorium men to keep abreast of medicine by spending time in general hospitals and to send general medical men to sanatoria.
7: To feed the public with the truth.
8: To remember always that tuberculosis is only one of many diseases and to develop our interests accordingly.

That dreamer was Allen Krause. His age was thirty-seven. His position (a recent appointment) was Associate Professor of Medicine, Johns Hopkins University, and Director of the Kenneth Dows Fund for the Study of Tuberculosis. To this position he had come after seven years in Saranac Lake where he had recovered from tuberculosis that gave him his scientific interest.

Born in Lebanon, Pennsylvania, February 13, 1881, into a Pennsylvania German family[2] of colonial stock that boasted establishment in America before 1750, this man passed through many of the experiences of the average boy and graduated from high school at age fourteen. He studied one year with a lawyer, one with an engineer and one with a physician before he entered Brown University in 1898. In three years he was graduated with his A.B. degree. He remained in Brown to obtain his Master's degree at age twenty-two. At the University, both Phi Beta Kappa and Sigma XI awarded him membership.

[1] Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] The forebears of these people were invited by William Penn in 1681 to settle in Pennsylvania. They came mostly from the farming districts of the Palatinate in Germany.

The Brown Yearbook of 1901 carried the following item on "Pretzels," as he was called: "With a pipe in his mouth and a Limburger sandwich in his pocket, he entered the University.... His specialty is brains and he is a keen man to argue with. When he leaves these dear old grounds, he will study the art of cutting people, not socially, but merely with a scalpel."

Following his medical inclination, he went to Johns Hopkins University and from it he received an M.D. degree in 1907. During these student years three traits characteristic of his make-up in later years had become well developed. These were his capacity for extensive and retentive reading on a large variety of subjects, his tendency to talk little about plans and activities before they were realized and his tendency to dominate a situation by a demonstration of knowledge superior to those about him. At Johns Hopkins he was comparatively nonconformist: he was known to be brilliant and of strong opinions. He spent a good deal of time with his books and thoughts and was not infrequently absent from class. He repaired often to Louie's on the corner for shop-talk over the beverage table. Yet his scholarship merited the Alpha Omega Alpha award and he finished fifth in his class of seventy-six.

At the beginning of his fourth year in Medical School he married Miss Clara Fletcher (October 10, 1906). To them three sons were born. Throughout the many years of their married life, Mrs. Krause virtually dedicated herself to him and his work. In her understanding way she shielded him from all but a bare minimum of distracting circumstances. She thus conserved to him many hours for work and was a silent partner in many a paper.

Upon graduation from Medical School Krause received an appointment as Assistant in the Department of Pathology under Doctor Welch. Here he exhibited an intelligent interest in the work and put forth more than average effort in the demonstration room, laboratory and library. He spent many hours at study with fellow workers and showed the beginnings of the investigative turn in which he was soon to become master.

About a year after this appointment he fell ill, with loss of weight and strength, followed soon by what he called intercostal neuralgia. He had had a little cough and expectoration for years. In December, 1908, he became a patient in Trudeau Sanatorium, with bilateral disease and positive sputum. His symptoms subsided promptly, almost dramatically. According to the record, he was very soon walking an hour each morning and evening and spending the remainder of the day and half the night with his books. He left the institution March 30, 1909, and attached himself to the Saranac Laboratory.

In this new position Trudeau and Baldwin won his admiration and affection and were a source of great inspiration. Soon he was devising and executing experiments: his knowledge of the field of tuberculosis first became extensive and, later, all inclusive. For seven years he worked. After a year his papers began to appear in the medical journals. Baldwin's work on hypersensitiveness and the work of Roemer in Germany became his theme song, variations and elaborations of which were to appear later and to be built into a neat concept. This

seven-year period of rare opportunity to grow and to develop ideas, technique and approach placed him in the top rank of research workers—yes, of authorities—in the field. So it was not strange that he should have been chosen as head of the Kenneth Dows Fund for the Study of Tuberculosis when it was established at the Johns Hopkins University in 1916 and thus he returned to the scene of his training with an established name, sitting in a high place in the research world with a vista of opportunity before him.

The going had not always been easy. A small salary and a growing family demanded frugal management and careful planning. In fact, he used to say that, on his arrival in Baltimore, his piano and library represented his entire possession. Fortunately, his tuberculosis never returned to plague him or to modify his life. But in 1914 he developed carcinoma of the rectum. An extensive Kraske operation, performed by Doctor Finney, with all of its discomforts and inconveniences, long days and weeks of doubt, uncertainty of the future born of a knowledge of the statistics regarding survival from this disease—these he weathered stoically and philosophically; these he suffered in truly heroic fashion; these he met with the determination to work while time allowed. These were still in his mind, though tempered by time, when he wrote down his ambitions in the letter to his friend quoted at the opening of this sketch. Who but one of heroic mind would lay out a program of such proportions when he knew that precious years must still pass before he could feel safe from metastasis.

Thus Allen Krause took over his new job, chastened by disease, seasoned in research, strengthened in knowledge by his omniverous reading.

What personal traits and what habits and interests characterized this man, so comparatively young when he assumed these duties? He was small; he had moderately prominent eyes which indicated keen interest in all about him. Personally gracious and friendly to all, he was an entertaining conversationalist who used his wide knowledge gained by reading or, as he called it, "fireside travel." He would sit far into the night and discourse delightfully on almost any subject. His chief interests were history, music and philosophy, and his preferred form of reading, biography. He seemed to forget nothing he had read; he had a remarkable capacity to associate and correllate time, place and circumstance of the subject matter in his knowledge. His genius lay in his ability to synthesize his fund of abstract knowledge and turn it to practical applications.

He put his visitors at immediate ease, but his extensive knowledge soon caused him to dominate the situation and to carry his listener far beyond and often far outside the chief interest that prompted the visit. Some who came for an interview left with the item aimed for discussion scarcely touched upon, so fascinated had been Krause's running talk. In general, however, the questioner obtained a clear answer to his query. He frequently punctuated his remarks by going to his book shelves for some pertinent reference, illustration or corroborative item. And invariably during an interview he "rolled his own" cigarettes which he smoked almost incessantly. His bag of Bull Durham and his little sheaf of cigarette papers he had always at hand.

Whether in a scheduled appointment, in an informal gathering, at dinner table in his home, in the hospital dining room, this characteristic of dominating the conversation through possession of extensive knowledge projected itself. In addition, he possessed a keen sense of humor, tended to "rib" his fellows at times, and was ever ready to relate a story to suit the occasion. To all this he referred frequently as "being blessed or cursed with the gift of gab."

He often read his recently written manuscripts to his visitors. At times, members of the Department who came in for a brief talk about some departmental matter would be regaled for an hour in conversation and literary entertainment which was always interesting but devastating in loss of time and efficiency in the clinic below.

Although very agreeable as a rule, he could be opinionated and arbitrary, especially about certain features of his own work and theories.

He was unorthodox both in his religion and his pathology, but a good many of his apparently "bizarre statements have come to have great weight in the present day." He once told Doctor Baldwin that his grandmother had planned him for the Lutheran ministry. "Such a career would seem anomalous from what we have known of him, as he certainly could not have accepted many dogmas laid down by the church. His agnosticism was reverent . . . but he would have been ready to talk out anyone who attempted to convert him."

In spite of his foibles, he stimulated and encouraged all who sought his advice. He overwhelmed first by his fund of knowledge, then he planted in the interviewer's mind the urge to do good work—superior work—and lots of it. His influence through personal relationship was large. In fact, his foibles so-called, his manner, tactics, ambition, energy and determination, all had a focal point in the engaging personality that was Allen Krause.

He approached his new position practically without precedent. Of the Medical Schools of the United States, few had a tuberculosis service worth the name. Except for the Phipps Institute of the University of Pennsylvania, none afforded a well equipped research laboratory for controlled experimental study, correlated with a clinical service: none could boast a well directed course of instruction encompassing the history of the disease, its diagnosis, its aetiology and pathology, its behavior and treatment. This is what Krause established in Baltimore. Years before this, Henry Phipps of Philadelphia had provided funds at the Hopkins to establish a tuberculosis clinic. To the existing small, two-story structure a third floor was added and equipped completely as a research laboratory. The entire unit became, technically at least, the tuberculosis service of the Department of Medicine with Allen Krause as Director. Actually he had but little to do with the clinic which was in the able hands of Dr. C. R. Austrian, but the work of clinic and laboratory were well coördinated and attracted selected students. Through this coördinated work Krause availed himself of the opportunity to seek clinical manifestations of principles pointed out by his experimental work.

The laboratory was opened only a short time before the United States entered the World War and did not get off to a good start. Three different physicians

took a brief turn at "research." Most of the interested or capable men were either in the service or were swamped with routine work made doubly hard because so many were off to the war. The two *Dieners* left the same day for the army. One day at Louie's Krause learned of a young German tombstone maker in the neighborhood who wanted work because, as an alien, his activities and movements had been limited and he was unable to travel from his home to his work-place. An interview brought Albert Lutz into the laboratory family, eventually to become the perfect laboratory worker. Soon he brought his aunt, Lena Fields, in for a job as charwoman and these two people lent color to the set-up.

Throughout the greater part of the war the laboratory had no physician on its staff except Doctor Krause. He found himself with much to do. The new laboratory and its work had to be carried on to justify its support.[3] For a part of the school year he had three clinics, one lecture and one conference a week and wrote 10,000 to 12,000 words monthly for a series of articles for The Journal of the Outdoor Life. In addition, he became secretary of the Laennec Society and of the Historical Club and he was Managing Editor of The American Review of Tuberculosis. As if possessed with limitless energy, he accepted several invitations a year to speak at meetings.

He was greatly disturbed over the way physicians and the Army were meeting the tuberculosis problems of the war. Especially did the tendency for able men in tuberculosis to go into the Army *to examine* recruits distress him. "I haven't time to detail my views on tuberculosis and Army routine," he wrote to one of these men, "but I do think that things are in an awful mess and that the . . . measures are extremely puerile and sophomoric . . . Predisposition, substandard constitution, fresh air, milk and eggs, universal tuberculosis, incipient diagnosis, signs in the chest (of what, pray), nutrition! ! ! Isn't it about time to make all these fellows toe the mark and *prove* exactly what they mean by such juicy mouthfuls? Let's make 'em answer: what is tuberculosis? You'd get a hundred damfool views. What causes tuberculosis? Truly the *bug per se* is the least important factor. Let's hammer in intercurrent respiratory disease, strain —physical and mental—pregnancy, accident. What is tuberculosis? All the fresh air in the world won't have the least effect *of itself* on tuberculosis *so long as strain is* kept up." In the same letter he remonstrated: "*Only don't stop studying tuberculosis* . . . Don't let this war put us back to where we were in 1890 . . . Your country may need you, it is true: but you can perform no greater or higher service to your country, to its Army, and to the world than by using every talent and every ounce of energy you possess to straighten out the tuberculosis problem and put it on a sane foundation. . . Whole-hearted study of the causes of consumption is more serviceable than years of examination of recruits."

[3] At that time he had in preparation papers on "what is tuberculosis?", America's work in tuberculosis (never published), studies on lymphatic transmission of tuberculosis, chronic protein intoxication and tuberculosis, the nature of resistance to tuberculosis, the acid-fasts, and on pathological anatomy.

As teacher, he shone in the lecture room. His well-nigh complete knowledge of the history of tuberculosis gave a fascination to his lectures which he delivered in direct manner and always without notes. He spoke with such speed that the best of medical stenographers failed to take down all he would say. Yet, with all the speed, his hearers on the back benches could catch every word.[4] His first lecture was attended by the students in the course. In his later ones he talked to a capacity house. His discourses were orderly: each one emphasized and re-emphasized just a few points and drove them home: each one was replete with abundant reference to the literature of several languages. In a single lecture he has translated directly a paragraph or more from Greek, Latin, German and French sources. Many quotations he gave as much to send the student to the literature as to enrich the subject matter.

His lectures and writings led to many invitations to address societies. He became a headline attraction. But he seldom showed any regard for time limits and sometimes monopolized the time allotted to other speakers. This was particularly conspicuous in the early days of the Trudeau School with the founding of which he had much to do. Scheduled for a one-hour lecture, he would often continue well beyond the allotted time. Since his subject matter was always interesting, the students would sit through the discourses. They would complain of their length, but ask for more.

In his laboratory teaching Krause emphasized two things always: *safety* to the operator, who must often handle living tubercle bacilli, and meticulous technique in the execution of procedures. He would don his protecting gown and demonstrate step by step the safe and proper manoeuvre in the procedure on the day's agenda and would follow with a very informal quiz. Then he would watch the student and help him until he proved his understanding of the process. An occasional student, after he had been drilled in procedure and had shown his ability to perform safely and well, was taken into the laboratory family for more intensive study and research.

The man's rare gift in the laboratory was his capacity to formulate experiments, single and in series, to test a certain point or two and then to execute them in complete detail. His notebooks were neat and clean and they carried a wealth of particulars. From the notebook the report of the experiment became, with the greatest facility, the manuscript which appeared in print. Krause the experimenter furnished material for Krause the writer. He had a faculty for taking a fact shown by experiment and describing it, elaborating it and placing it properly in relation to other facts and then to tell the story in as perfect English as graces medical literature anywhere to-day.

[4] He spoke often of his "patella clonus" just before and at the beginning of a lecture, and he admitted that he always felt uneasy until he had got well into the matter. He described his feelings on at least one occasion when he was to make an important address: "Beforehand I was a little bit afraid of what I might be getting into if I took up this subject ('what is tuberculosis') with the men, but after I got on my feet I found that I was in unusually good form and it went off very easy for me."

His appreciation of fine work is shown not only in the language of his published work but in the quality of the accompanying illustrations. Throughout the life of the Dows Laboratory he had an able artist on the staff. The first of these was Dorothy Peters, the second Hermann Becker. The work, especially the colored drawings, of these two embellish and add to the value of many of the papers originating in the laboratory.

From his laboratory came work on a large variety of subjects. Of these, that dearest to his heart and that which will long represent the scientist Krause at his best, is his work on immunity and allergy in tuberculosis. In a long series of critical experiments, executed over a number of years by him and his associates, he established facts with which he built an understandable and rational explanation of the *modus operandi* of these two phenomena. Exception has been taken to certain features of this work, but criticism has centered on interpretation not on revealed fact. Throughout this he stood confidently and quietly on the record. This large body of work stands out in bold relief in our conception of the nature of tuberculosis.

His daily routine in the laboratory was his own and was not in conformity with the average among his fellows. His office routine saw him arrive about ten in the morning, look over his mail, hold a pre-arranged interview or two, work over manuscript or proof for the Review until noon.[5] His lunch he kept in the laboratory ice-box, for he ate in the hospital dining room only occasionally. Each noon he took down his specially cleaned, half-liter beaker,[6] a triangle of cheese, a few crackers and his beverage and ate his meal in the quietude of his own office as he read or worked. Luncheon over, he did whatever was necessary in the laboratory—examined one lot of guinea pigs, tested another lot or weighed them. If no lecture was scheduled, he would leave early—his bag invariably crammed with manuscripts. He had a penchant for working full time on holidays—days when interruptions would be negligible.

In the field of medical writing Doctor Krause far outstripped his fellows. His writing often approached art. His manuscript was composed with such care that the final article as printed represented almost word for word the first (and usually only) draft. Attention to paragraph structure and content, to continuity of subject and subject matter, to sequence of sentences, to the choice of words and especially to the choice of verbs produced a finished product as attractive, as gripping, as clear, as limpid and easy to follow as that of any contemporary in American medicine.

But he required certain conditions for contemplating and writing, most of which was done at home. He had to be in his study and the household had to be quiet. When the going was good, he would spend hours at his desk without let-up but for coffee or beverage, or a turn at the piano which he played with skill.

Before actually beginning to write, which he did rapidly and in a half-print hand, he spent hours and days turning the points over in his mind and, it ap-

[5] See page 603.

[6] Always kept clean by Lena who also maintained the stock of liquid refreshments.

peared, arranging them in their logical sequence. At this stage his library table[7] might be littered with books opened or marked for reference. But when he began to write, the ideas and words flowed freely and, as stated, the original manuscript often represented, verbatim, the printed word. His *magnum opus*[8] delivered at the Fifth Conference of the International Union against Tuberculosis contained upwards of 15,000 words, and the total elapsed time required for writing was only four and one-half days.

His was no life of ease. It cost the man hours of gruelling work at the library table—the more difficult because of the brace and pad made necessary by the colostomy left at operation. When weariness of body appeared and the urge to stop forced itself upon him, determination dominated and the work went on. About these physical difficulties he seldom if ever complained.

He recognized that the criticism of repetition had been aimed at some of his writings, notably his series of papers in The Journal of the Outdoor Life. Said he, "I've learned that in teaching or writing exposition, success consists not in telling everything known about a subject, but in picking out what you need in your business and hammering away at these few points. This is exactly why Popsy Welch is such a wonderful lecturer. He builds a structure: he does not pile up a junk heap."

What of this man's writings? Look at his bibliography: 187 items in twenty-eight years; 162 of these came from his pen during the period from 1909, when he found his stride at Saranac Lake, to 1929, when he left his active laboratory work in Baltimore—an average of eight papers a year, and not a dud among them. No value is to be placed upon volume alone in medical writing nor merely upon the number of papers produced a year. At the risk of being trite it may be said that quality and not quantity is the measuring rod of a man's true productivity and true influence in his field. Any hack-writer could turn out a large volume of work in twenty-eight years. But these papers of Krause invariably present a new fact, a logical deduction from work recounted, a rounding out of a conception, a new gem from old literature, a neat biographical story.

Almost coincident with the establishment of the Dows Fund and the Krause appointment at Baltimore, the National Tuberculosis Association created an official journal to be known as The American Review of Tuberculosis. The Association named Doctor Krause as its Managing Editor. Its editorial board[9] placed full responsibility upon the Managing Editor[10] for the content, make-up,

[7] A treatise would be required to describe his library, with an analysis of his selection of favorites. The library represented his penchant for first editions, particularly of literary and historical classics of England of the eighteenth and nineteenth century. He ranged many fields, bought many handsome volumes and gave them loving care.

[8] *The Anatomical Structure of Tubercle from Histogenesis to Cavity*, American Review of Tuberculosis, 1927, *15*, 137.

[9] Dr. E. R. Baldwin was Editor-in-Chief.

[10] The title was changed in 1922 from Managing Editor to Editor and the title Editor-in-Chief was dropped. Doctor Baldwin became a member (and still is) of the Editorial Board.

editorial policy. This he accepted. He swung into action and Volume 1, No. 1, appeared in March, 1917.[11]

The Managing Editor took excessive care in putting out the journal. His ambition was that all statements be accurate and clear and that there be no mistakes. He read and reread manuscript; printed all good papers that came in and some that were not so good—his guiding principle in selection being, in part at least, apparent promise in the author and apparent honesty of purpose. He rewrote many sentences, paragraphs and (almost) papers. If he thought it was necessary to make drastic alterations he, of course, returned the original, redone or rearranged article to the author for approval, but many changes were first seen by the author in galley. In all changes, he strove for clarity: never did he endeavor to alter the meaning of the author. He strove to improve the quality of the author's work, to invite or urge him to come back with more. If a paper was unsuitable or could not be tailored to fit, it was returned to the author with a simple, direct statement of its unsuitability. He did not fail to return a paper to a well known author if it appeared unsuitable.

So earnest was he in his efforts to have the Review free from mistakes that he even verified the references in all articles published in the first several volumes. As time went on, however, and the Review grew, he no longer assumed this rightful responsibility of the author. But even as late as 1929, when he left Baltimore, he made up the cards for the Index of each volume. This he made complete—a separate reference for each important word in the title as well as one for the author. And he checked the galley meticulously. His instructions to the printer were detailed and clear, and he was always impatient with printer's errors and especially with his failure to keep to his time table. If the Editor sometimes drove the printer, he drove himself more. He loved the Review and labored over it.

From the first issue of the Review its quality was implicit in make-up and content. Throughout its twenty-three years under the Krause Editorship, that quality remained high, and the Review ranked among the best of the medical journals at home and abroad. It stands as a memorial to the ability, imagination, industry and genius of its Editor.

He made quite a picture at his Editor's desk, with long shears hanging conveniently from a hook on the corner, a jar of paste always handy, a sheaf of brown wrapping paper on which he could paste items, requiring indication of size of type, such as headings, footnotes, legends, etc., which was to be different from that of the regular page. He had a stack of incoming manuscripts on one side and a wire basket full of accepted, connotated papers and folders of proof for the printer on the other.

Perusal of manuscripts for the Review laid a considerable burden upon Doctor Krause's eyes. At one time he developed marked, fluctuating refractive error and photophobia that forced him to remain in comparative darkness for several

[11] In addition, he acted for years as Editor of the American Section of the English publication Tubercle.

weeks. During this time his secretary or associate sat for several hours a day in one corner of the darkened bedroom with a small sub-stage lamp as the only source of light and read page after page of manuscript, made suggested notations and changes and again read the altered product. Copy had to be delivered to the printer for he could not know how long this new and cruel disability might continue.

The Dows Fund represented a five-year grant. It was renewed for two successive five-year periods. The last renewal in 1926 specified no further extension. In 1929, an attractive offer to Doctor Krause to become President and Director of the Desert Sanatorium and Institute of Research at Tucson, Arizona, found him interested. He weighed his Baltimore situation against the new offer. He saw continuation of the Associate Professorship but inevitable curtailment of his laboratory layout and program. He visited Tucson and there found what appeared to be a seat of fruitful labor. To Tucson he went.

Altogether he had done a masterly job in Baltimore, as teacher, editor and investigator. The new position was essentially an executive one and a distinct departure for him. But he continued the Editorship of the Review. His bibliography still grew but at a much reduced rate. His presence on the lecture platform was still demanded. Such requests were sufficiently numerous in 1930 for him to set up his own schedule which required "almost six weeks of gallivanting through the Pacific Coast states from Butte to San Diego." He seemed to take it all in his stride until his own ill health and the inroads of the depression upon the Sanatorium appeared. These grew and led eventually to his resignation and return to Baltimore in 1936.

In Baltimore again, he had editorial rooms in the Johns Hopkins School of Hygiene and Public Health, for he continued to edit the Review. A few months after his return, his illness encroached further on his strength. In another few months he had to take to his bed and he never rallied sufficiently to resume work. He died on May 12, 1941.

What evaluation will men put upon this man? Each one who has known him will see him from a different angle and rate him according to his own judgment. But it is of interest to ask what he thought of himself and his work. We know too little of this except from a few of his letters, written on a rare occasion when he was in a confidential mood. These indicate his estimate of himself and the conception he had of what he was trying to do. "I have set out to paint a large canvas: to write a piece of literature and interest the intelligent person." . . . "Don't misjudge me. . . I'm not discouraged about myself or about my work. And as long as I feel that I'm honest and am working for a purpose, I'll never be. I'll acknowledge that I like perfection and strive for it and lose interest in the sloppy worker and thinker: and some think me a knocker because I won't come across when mob psychology gets under way and steps to the footlights. But *my own opinion of my own opinion* is perhaps just a little less exalted than many imagine. I can only say that it has taken me years to acquire enough confidence

to push myself and . . . only recently I have decided that if things are to move, if certain well defined ideas . . . are to be put through, then a lot is up to me and I must push them."

In 1931 the National Tuberculosis Association awarded him the Trudeau Medal—the highest distinction it can confer. The citation reveals well in what esteem he was held. "As a pathologist of unsurpassed reputation, he has studied tuberculosis in all its forms and relations. As an author and editor of scientific articles and journals and as a lecturer to the laity he has disseminated knowledge concerning the causes, treatment, and prevention of tuberculosis, and in this connection has developed tuberculosis thought as much as any man in the country to-day. As a physician, he has encouraged prevention and the scientific treatment of tuberculosis. As an educator, he has stimulated the work of various antituberculosis agencies throughout the country, coöperated with other health organizations and promoted international relations in connection with health activities in the study and control of tuberculosis."

It is difficult if not impossible to indicate the influence Doctor Krause exerted on tuberculosis work.[12] His wise counsel, often sought, was always sound. The high quality of his own published work must have stimulated many an author to make his writing of better quality. His standards must have set a goal for many a writer. His range of interest, which included all of medicine, prodded his students and fellow physicians to broaden their horizon and to widen their point of view. He caused people to appreciate the historical aspects of medicine and awakened in them an interest in medical literature as art. He sent people to the literature—ancient and modern—and touched off cultural interests in many. But his personal contacts with many of the younger, rising men in his field inspired them, encouraged them, urged them on to basic work and sound growth. These contacts came through correspondence, friendly meeting, counsel, comment on work in progress and publication of work. He took great pride in the accomplishments of the younger men in his broad entourage.

[12] Some idea of the range of his interests and extent of his appointments and connections may be seen from the following data as listed in American Men of Science (1938 edition, in which he is starred): Medicine. Lebanon, Pa., Feb. 13, 81. A.B., Brown, 01, A.M., 02, 02-03; M.D., Hopkins, 07; hon. Litt.D., Norwich, 35. Asst. and instr. path., Hopkins, 07-09; asst. director, Saranac Lab., 09-16; assoc. prof. med., Hopkins, 16-29, lecturer, 29; pres. and director, Desert Sanatorium, Tucson, Ariz., 29-; clin. prof. med., Stanford, 29-; Southern California, 32-; Director, Dows tuber. research fund, Hopkins, 16-29, visiting lecturer, 30-; Assoc. physician, Hopkins Hosp., and physician in charge, Phipps tuber. dispensary, 16-29; lecturer, Trudeau Sch. Tuber., 16-29. Managing ed. 'Am. Rev. Tuber.,' 17-22, ed. 22-; Am. sect. 'Tubercle'; collaborator, 'Ztschr. für Tuberk'; 'Arch. medchirurg. de l'appareil respiratoire.' Advisory board, Colo. Foundation Study Tuber.; Northwoods Sanatorium. Trudeau medal, Nat. Tuber. Assn., 31. A.A.; Am. Physicians; fel. Col. Physicians; Tuber. Assn. (director, 17-20, 26-, research cmt); hon. mem. Soc. Clin. Invest.; Assn. Anat.; Assn. Study Int. Secretions; Pub. Health Assn.; Assn. Path. and Bact.; Soc. Bact.; Soc. Exp. Path.; hon. mem. Harvey Soc.; Clin. and Climat. Assn.; fel. Am. Geog. Soc.; hon. mem. Interurban Clin. Club; Pacific Interurban Clin. Club; Ariz. Anti-Tuber. Assn. (director); hon. mem. Los Angeles Clin. and Path. Soc.; Int. Union against Tuber.; Int. Soc. Crippled Children (cmt. prev. and research). Infection; pathology, immunity and epidemiology of tuberculosis; nontuberculous pulmonary infections.

Through his own research, his high standards, his personal contacts, his teaching and his editorship, his influence will continue to bear fruit for a long time to come.

The author cannot close this fragmentary account of his friend without acknowledging the great value of this friendship and his appreciation of this master workman. From medical school days on Doctor Krause proved many times to be an understanding and helpful adviser, counsellor, father confessor, friend. He stimulated when stimulus was needed; he cautioned when use of the brakes was indicated; he advised when his judgment was sought; he helped as a friend, always.

ACKNOWLEDGMENTS

Although much of the content of this story represents recollections and impressions from over ten years of close contact with Doctor Krause, much has come from others who have known him better than I and from letters which have been loaned to me. In particular I wish to thank Mrs. Krause and Dr. E. R. Baldwin for exceedingly helpful suggestions and for reviewing the preliminary manuscript. Drs. Charles R. Austrian and Max Pinner, both long and warm friends of Doctor Krause, have extended critical help that has improved the original materially.

ALLEN KRAUSE AND THE NATIONAL ASSOCIATION

KENDALL EMERSON[1]

National health or welfare agencies do not flourish merely by virtue of a successful launching. True they must have a worthy purpose and this must be backed by founders of vision, integrity and distinction. But this is not enough. Into the warp of their fabric there must be woven a continuous woof of personalities of equal vision, of like devotion and even more distinguished. The growth and service of the National Tuberculosis Association exemplify this principle.

Allen Krause was one of that army of physicians who fell prey to tuberculosis in line of duty. As in the case of many colleagues affected with this preventable disease, he developed a life interest in its control. From then on it became and remained one of his major preoccupations. His keen mind promptly grasped the fact that responsibility lay with the medical profession and that there was a paucity of knowledge among doctors regarding the disease itself, its epidemiology and the methods to combat it. One result was THE AMERICAN REVIEW OF TUBERCULOSIS, which, under his guidance, gained and maintained its present reputation among the world's scientific medical journals.

Doubtless, too, the unorthodox behavior of the tubercle bacillus intrigued his enquiring mind. This led to his classical studies of allergy and immunity which still stand as a tribute to his capacity as both a scientist and a logician. Throughout his career these qualities enabled him to sift the grain from the chaff and placed his writings among the great contributions to the knowledge of tuberculosis.

What Allen Krause accomplished in the academic world and in scientific circles, however, will be amply set forth elsewhere. This note is in tribute to his loyal service to the National Tuberculosis Association and especially to the National Office itself. Due to ill health his visits during the latter years became infrequent. Earlier, however, he was welcomed more often and always with enthusiasm. At times he came unheralded and quite casually to discuss matters connected with the Review, the Annual Meeting, the medical research program or international affairs. If one member of the staff was absent or busy another would do. There was never a dearth of topics for discussion in his fertile mind. He knew every one and nothing pleased him more than to meet an opinion differing from his own and inviting argument and discussion. This was usually rather one-sided because of his encyclopedic knowledge and his ability to cite the authorities on the subject in hand.

These dialectical excursions were by no means limited to tuberculosis or even the field of medicine. They ranged the broad realm of human interests including education, music, art, literature and even politics. His absorption in the publication of the Review carried him deep into the printer's trade. He quickly

[1] Managing Director, National Tuberculosis Association, 1790 Broadway, New York, New York.

mastered those small refinements that create the difference between a superlative production and merely a good journal. From then on, under his guidance, the Review never slipped from its position of conspicuous excellence. In business, too, he showed an instinctive grasp of the tough problems that arose during the hard years of the early 'thirties.

His chief avocation, however, sprang from his innate love of books. His manner of encountering a new book was one of inquiring respect. It took but a moment for his keen mind to classify the volume and in that time it was possible to watch his interest swing toward reverence or apathy as the content deserved. The affection he bestowed on his own collection of rare volumes and first editions is familiar to those who visited his home. Not outwardly emotional and somewhat off-hand in displaying these, he still revealed the soul of an inveterate bibliophile in his gentle handling of his treasures and his clear appreciation of the outstanding merit of each example.

Allen Krause was one of those great personalities who for many years helped to weave the pattern of the National Association. Added to his scientific interest in tuberculosis was the conviction that popular knowledge regarding the disease was of high importance and that existing social inequalities and substandard living conditions must be attacked before it could be brought under control. The workers at the National Office were perhaps most conscious of this. To them it was given to recognize in him that deeper human sympathy and friendship which was not dimmed by the brilliance of his scientific achievement.

THE DYNAMICS OF EPIDEMIOLOGY IN RELATION TO EPIDEMIC TUBERCULOSIS

IAGO GALDSTON[1]

Die richtige Fragestellung das ist mit das grösste Kunststück in der Wissenschaft.—Carl Weigert

The intelligence of Allen Krause was distinguished above all by its catholicity. Krause had the happy faculty of acquiring an understanding of the universals of a science while groping among its minutiae. He prized the objective study of the particular, but he seemed never to become ensnared in the threads of singular knowledges. In ripe time he managed to weave them into a pattern to make a fabric of them. This catholicity of his intelligence is best revealed in those essays in which Krause reviews and summarizes the current knowledge on tuberculosis. *The Evolution of Tubercle* is of such quality, so too are his essays *Environment and Resistance in Tuberculosis*, but most notably, Krause's essay *Tuberculosis and Public Health* which was the 1927 Hermann M. Biggs Memorial Lecture delivered at The New York Academy of Medicine. Covering large fields of thought, these essays are written with a compactness that mirrors the author's being. They are vibrant with the energy of a strong and disciplined intellect. Within the text one comes across terse, nut-like sentences, complete in themselves, suggestive as well as provocative of larger thoughts. One such sentence is to be found in his essay on *Environment*; it reads as follows: "Environment includes every mundane experience which directly or indirectly, may exert an effect on the constitution and function of tissues," (14). This is a pregnant sentence, fitted to serve as a pivot for the orientation of fundamental questions on epidemiology in general and on the epidemiology of tuberculosis in particular.

Every earnest student of tuberculosis, clinicians, or public health workers, must sooner or later come to grips with these matters, for, far from being of an academic nature, they are vital to our effective understanding of and to our effective dealing with the disease.

The epidemiology of tuberculosis has been much labored by many men. There is a profusion of data on the subject, but these data do not yield a neat or impressive summary. In many respects they seem to form a maze rather than an organic pattern. The emphasis they afford now falls on the parasite, now on the host. Some yield the seeming conclusion that the soil is the crux of tuberculosis; others, that environment, expressed in terms of occupation, nutrition and shelter, is the determining factor in the spread and the virulence of the disease. There have been and there are among us partisans of many schools, each with a unique solution, based upon some singular understanding of the epidemiology of tuberculosis.

This seeming confusion is however understandable. It arises from the use

[1] The New York Academy of Medicine, East 103rd Street, New York, New York.

of one term in many connotations. Epidemiology is now a protean science. We have pathological, statistical, immunological, anthropological, historical and experimental epidemiologies.[2] Too frequently each is presented as *the* epidemiology of tuberculosis. There can be no doubt that the data presented have a bearing on the epidemiology of tuberculosis, that they can illuminate the subject. But in and by themselves they do not constitute *the* epidemiology of tuberculosis.

The history of a disease is not its epidemiology, though it can and frequently does indite the times during which it was epidemic. The pathology of a disease merely helps us to understand why a disease becomes epidemic under certain circumstances. Statistics, like history, offer demographic data on epidemiology, and gauge its duration and intensity, but afford no greater insight into the essentials of epidemiology than a fever chart does into those of pyrexia. Anthropological studies are generally too complicated and too incomplete to reveal more than the determined prevalence of a disease among a given people. Experimental "epidemiology" can show no more than the propagation-dynamics of a disease within a herd living in an artificial environment.

All of the above named disciplines afford to epidemiology valuable data. But Epidemiology is the creative discipline which integrates these data, according to its own laws to produce an intelligible science of the epidemiology of diseases. In this sense there is a distinctive science Epidemiology and, also, particular epidemiologies of particular diseases.[3]

Epidemiology so understood is the study and science of the epidemic diseases, those indwelling among the people, determinant of all the causes that render the disease epidemic in extent. Epidemiology then is the science of the aetiology of epidemics. It seeks to answer the basic questions as to what factors operate to extend the prevalence of a disease to epidemic proportions.

There are distinctive advantages to the above given interpretation of the meaning of epidemiology. The first perhaps in the clear demarcation set between the aetiology of the disease proper, and the aetiology of the epidemic

[2] Stallybrass considers epidemiology as "the science of infective diseases, their prime causes, propagation and prevention. It deals more especially with their epidemic manifestations."

W. H. Welch has defined epidemiology as "the natural history of disease."

Dudley indicates practically the same thing in the statement: "The epidemiologist is a medical ecologist."

The American Epidemiological Society has defined epidemiology as "the science which concerns itself with the natural history of disease as it is expressed in groups of persons related by some common factors of age, sex, race, location or occupation, as distinct from the development of disease in individuals."

W. H. Frost's definition adapted from Hirsch is: "The science which will give, firstly, a picture of the occurrence, the distribution, and the types of the diseases of mankind in distinct epochs of time and at various points of the earth's surface; and secondly, will render an account of the relations of these diseases to inherent characteristics of the individual and to the external conditions surrounding him and determining his manner of life."

(From: Wilson G. Smillie: Public Health Administration in the United States, Second Edition, New York, Macmillan Company, 1940, p. 182.)

[3] For references see Selected Bibliography.

manifestation of the disease. By implication the dynamics of the one are distinct from the dynamics of the other. Epidemiology can be considered apart from the mechanisms of the disease operating in the affected individual. It may even be possible, as it frequently is, to overcome the epidemic extension of a disease without in any way affecting the morbidity of the disease.

It can be further hypothecated that while the aetiology of a disease may be specific, the aetiology of its epidemic extension may be generic; that is, the epidemiological dynamic factors may be common to several unrelated specific diseases, such for example as rickets, tuberculosis and syphilis. Finally it is highly suggestive that epidemiology derives its most important data from a study of environment—environment understood in the meaning given to it by Krause.

It will be of interest to consider the epidemiology of tuberculosis in the light of the above given premises. This will serve to illustrate the thesis and perhaps to shed some new light on tuberculosis as an epidemic disease.

On the score of the latter, it is pertinent to observe that while tuberculosis as a morbid process has prevailed since the earliest times in known history, there is no warrant for assuming that it always prevailed in epidemic proportions (1). Krause in his Hermann M. Biggs Memorial Lecture aptly observes:

> "From much that is said and written we get the idea that, ever since its first diffusion throughout the civilizations of old, tuberculosis, until yesterday, reigned chief among mortal diseases, settled as a pall over all human effort that aspired to the higher reaches of community existence; . . .
>
> ". . . But is this doctrine of the uninterrupted hegemony of tuberculosis correct?
>
> "We are inclined to doubt it because it will not fit in with the facts of the social history of Europe. The more fully these are coming to light the more there is emerging the likelihood that, after the wreck of the Roman Empire, there must have been long periods when tuberculosis was in relative abeyance, if indeed it did not entirely disappear, in regions where it had once been prevalent" (16).

Epidemic tuberculosis was probably nonexistent before the seventeenth century, with the possible exception of brief periods during antiquity and in limited localities, such as Athens, Alexandria and Rome. The epidemic tuberculosis with which we are acquainted is of modern origin and is coterminous with the development of the modern industrial system. This has been recognized by many and is summed up by Cobbett in the dictum Tuberculosis spreads *pari passu* with industrialism (3).

While historically the time parallel between the rise of modern industrialism and of epidemic tuberculosis is closely approximate, it is not correct to deduce therefrom, as many are inclined to do, that there is a specific causative relationship between industrialism *per se* and epidemic tuberculosis. Industrialism can conceivably operate without bringing in its wake epidemic tuberculosis; and, epidemic tuberculosis can and does prevail in communities without any, or of only backward industrial development.

The causative factors of epidemic tuberculosis are independent of industrialism. Historically they were and are associated with and even related to industrialism, but the relationship was and remains more of a socio-ethical than

of a technological nature. An enlightened, intelligent, moral people with a social conscience could have managed the industrial revolution without having been obliged to pay the dreadful penalty exacted by the White Plague (12, 13).

Let us scrutinize these matters closely. The industrial revolution, as witnessed in England, involved a number of profound and radical changes in the economy and social organization of the land and its people. The principal ones were: the enclosure acts which deprived the common man of his rights to graze his cattle on the "commons"; the reform in agriculture which, though improving the yield of the land, helped to convert agriculture from a pursuit of family husbandry into a large-scale industry; the introduction of machines to replace hand tools; the utilization first of water power and later of steam power; the shifting of large masses of population from rural to urban centres; the rise of industrial communities, crowded factories and abysmal slums; the creation of a new social class—the proletariat, possessed of only one commodity, its labor power. These are the chief episodes of the industrial revolution and they have become the common knowledge of every man. But they carry certain secondary effects which are less commonly appreciated and which indeed must be known if one is to grasp clearly the reasons for the catastrophic effects of the industrial revolution, and more particularly why tuberculosis, together with other diseases, became epidemic during this period, and as a result of its qualities.

In the industrial revolution humanity experienced an unparalleled dislocation in most of its vital relations, never before in man's history was there such population density, such prolonged and close compaction of persons in factories and slums. The industrial revolution removed large masses from the soil, distanced them from their food sources, changed their diets, altered their foods, bound them by an exacting discipline to a toil never before experienced. The industrial revolution broke up the rural community, disrupted the homestead, dismembered the family. It changed no less the social and ethical relations. Old values lost their validity, old relationships their force and strengths. And because of all this, by this and through this, tuberculosis became epidemic. So, too, did other diseases, notably *cholera infantum*, typhoid and diphtheria, not to mention certain disorders of the psyche.

It is highly important to bear in mind that the social and economic dislocations experienced during the industrial revolution *were* historically associated with the development of industrialism, but these may not be taken as the inevitable concomitants of industrialization. Further, not industrialization *per se*, but its *historically* associated concomitants constituted the aetiology of epidemic tuberculosis. Any such combination of social, economic and cultural dislocations, no matter with what order of historical events they may be associated, will serve as *the aetiology of epidemics*, and commonly of epidemic tuberculosis.

Bushnell has shown that such was the case when the Negroes were liberated in the United States, at which time they experienced, particularly in the South, profound social and economic disorientations (2).[4] There can be no doubt that

[4] George E. Bushnell: "There can be no question that before the Civil War the Negro

the changes affected in the economies, social organizations, etc. of the peoples and countries conquered by the Nazis will and are serving as dynamic factors in the aetiology of epidemic tuberculosis, and of other diseases.

Such considerations shift the focus of attention from the pathogenic organism to the environmental factors. The shift is desirable, but it does not involve the preclusion of the pathogens from the purview of the problem of epidemic manifestations. The pathogens cannot in the light of our presentation be considered, as too commonly they are, malicious aggressors who by their own powers and momentum attack the masses and prevail against them in epidemic dimensions. But it can be postulated, and it has been demonstrated, that the pathogens likewise are affected by the socio-economic forces that affect society. Up to a measure the effects on the pathogens are of an inverse nature to those suffered by the higher animals upon whom they prey: they thrive as their hosts are less able to meet their onslaught. Yet all in all it is not the pathogens that play the determining rôle in the engenderment of epidemic diseases, but rather the environmental factors of the susceptible sufferers.

The recognition of this must prove of large consequence to public health and ultimately to the social economy. Confronted by disease of epidemic proportions an enlightened epidemiology will not confound the treatment of the disease in the affected individuals with the "treatment" of the aetiological factors of the epidemic manifestation. Nor will such an epidemiology mistake the specific cause of the disease for the specific cause of the epidemic. Nor yet again will the *outbreak* of a disease, trichinosis, botulism and the like, be considered the equivalent of an epidemic, in the sense of epidemic tuberculosis, epidemic syphilis or epidemic rheumatic fever.

In such an understanding of epidemiology, the term epidemic disease will not be restricted simply to the infectious and communicable diseases. It will be recognized that rickets is epidemic, so too are caries, arthritis and schizophrenia.

Best of all public health will not be, as to a large extent it is to-day, devoted to the sisyphusian task of attempting to deal with epidemic diseases, without awareness of or regard to those epidemic engendering forces whose manifestations are no sooner repressed in one form of morbidity than they reappear in another.

* * * *

This theme, the epidemiology of tuberculosis, was dear to the heart of Krause, and was the Benjamin of his intellectual progeny. With what earnestness he conceived of this problem, with what breadth he sketched its embrace, with what keenness he penetrated into its implications may be witnessed in his essay *Tuberculosis and Public Health*. Doctor Pinner who was for so many years intimately associated with Krause, informs me that it had been Krause's fond hope to crown his life's work by developing fully the substance he at best had

was in the same condition as respects infection with tuberculosis as the whites, in other words, he was tuberculized practically to the same degree as his master; the almost identical mortality-rate in the two races proves this beyond question. The frightful mortality after emancipation must therefore be explained on other grounds than that of the primary infection of a completely non-immunized population."

only sketched in his Biggs Lecture. That crown was unfortunately denied him. Yet in fondness it is pleasing to fancy that Krause even now has cognizance of these matters which we, who were his friends, are privileged to contribute in his living memory. I can fancy him saying "Yes, but," as he was wont to when he was still in our midst.

SUMMARY

Krause defined environment as that which "includes every mundane experience which directly or indirectly, may exert an effect on the constitution and function of tissues." The rôle of environment in the epidemiology of tuberculosis has been variously interpreted. This is largely due to the fact that epidemiology itself is endowed with a variety of meanings. The definition of epidemiology as *the science of the aetiology of epidemics* is advanced, and the rôle of environment, as defined by Krause, is accordingly evaluated, with tuberculosis as the particular example. Epidemic tuberculosis is of modern origin and is coterminous with the development of the modern industrial system. Industrialism itself is not, however, "responsible" for epidemic tuberculosis. The important aetiological factors of epidemic tuberculosis were the hygienic, social and economic concomitants of industrialization. Wherever these or similarly inimical conditions prevail, epidemic tuberculosis and other diseases in epidemic proportions are likely to prevail. The appreciation of the *aetiology* of epidemics apart from the specific cause of the disease involved is essential for the effective control of epidemic diseases.

SUMARIO

Krause definió el ambiente como lo que "comprende toda experiencia mundana que directa o indirectamente pueda ejercer algún efecto sobre la composición y función de los tejidos." El papel del ambiente en la epidemiología de la tuberculosis ha sido objeto de varias interpretaciones, debido en gran parte a que la epidemiología misma reviste varios significados. Propónese como definición de la epidemiología *la ciencia de la etiología de las epidemias*, y justipréciase a esa luz el papel del ambiente según lo definiera Krause, tomando como ejemplo específico la tuberculosis. La tuberculosis epidémica reconoce origen moderno, y es contemporánea del desarrollo del moderno sistema industrial, aunque el industrialismo mismo no es "responsable" de ella. En la tuberculosis epidémica los importantes factores epidemiológicos son los elementos higiénicos, sociales y económicos que acompañan a la industrialización, y siempre que existan éstos o semejantes factores adversos, probablemente alcanzarán proporciones epidémicas la tuberculosis y otras dolencias. Para el dominio eficaz de las afecciones epidémicas es indispensable conocer la etiología de las epidemias, aparte de la causa específica de la enfermedad dada.

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THE WAR AND TUBERCULOSIS

ESMOND R. LONG[1]

The world conflict of 1914–1918 for the first time revealed tuberculosis as a major war problem. From the early discovery of large numbers of tuberculous troops in the French army to the final assemblage of mortality records of the war years in the civilian population of all the countries engaged, it was evident that tuberculosis was exacting a great toll, unrecognized in the wars of previous years. Pestilence in mobilized troops has been familiar since early times and the disastrous spread of contagious diseases from armies in the field to the population not participating in actual hostilities is well known. For hundreds of years waves of typhus fever, plague, cholera, smallpox, dysentery and typhoid fever have broken out in warring nations, decimated armies and spread malignantly through the populations of the opposing lands (1). Until recently sickness always surpassed battle wounds as a cause of mortality in contending armies.[2] But in the presence of overwhelming mortality from acute transmissible disease in the armies of other wars and a current normal high tuberculosis mortality in the civilian population before 1914 a rising tuberculosis rate as a consequence of war was not clearly evident.

There is every reason to believe, however, that long wars accompanied by privation have always led to increase in tuberculosis. When distress has been extreme the effect has been clear. The siege of Paris in 1870–1871 led to a series of epidemics of acute disease and quadrupled the general mortality in six months. In the augmented number of deaths a large increase in tuberculosis was noted.[3] It is said that even the character of the tuberculosis changed from chronic to acute form (2). The more recent epidemics of tuberculosis in Warsaw and Belgrade in the late years of the first world war furnished a terrible example of fatal rise in phthisis in beleagured and conquered cities. The tuberculosis mortality in Warsaw increased from 320 per 100,000 before the war to 975 in 1917. With recorded increases all over Europe varying from 10 per cent in favored regions to more than 200 per cent in the most seriously affected, and with persistence of the rise for at least two and sometimes five years, it is evident that war tuberculosis cost Europe many thousands of lives. Statistics for 380 cities of more than 15,000 population in Germany alone, showed an increase from an average mortality of 157 per 100,000 in 1913 to 287 in 1918 (3). It would probably be conservative to estimate a rise of 15 per cent in tuberculosis mortality for three years in all Europe, which would credit the war with about 200,000 tuberculosis deaths.

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[2] Statistics from the Civil War list 304,369 deaths in the Northern forces, of which 93,433 were due to battle wounds and 186,216 to disease (J. K. Barnes: The Medical and Surgical History of the War of the Rebellion, 6 vols., 1870–1888).

[3] But, as H. Sueur wrote (Étude sur la mortalité à Paris pendant la siège, Paris, 1872), it would be impossible to determine the true mortality from phthisis because many deaths from this cause must have been included in the list of deaths from pneumonia and especially bronchitis.

The explanation of the increase in tuberculosis in Europe during the first world war has been the subject of extended research. Crowding, malnutrition, excessive exposure to infection and hardship of every sort have been considered by various students as responsible in different degree. One of the ablest analysts in the United States, Allen Krause, listed numerous causes of breakdown with tuberculosis, and warned against a narrow view and superficial acceptance of one or another of the several possible causes as solely responsible (4). "If anything is certain," he wrote, "it is that the curve of incidence of morbid tuberculosis will run closely parallel with comparative deprivation of the means of subsistence, and all the overstrain, exposure, faulty living and misery which accompany inability to live comfortably." In his well known masterly reconstruction of the world history of tuberculosis (5) he pointed out two other significant facts in the war epidemiology of tuberculosis, the immediacy of rise in the incidence of the disease with radical disturbance in a country's socio-economic structure, and the sweep-like result of the increased mortality as reflected by the prompt drop to less than the prewar rate with the restoration of normal conditions.

The world is now engaged in another war which already has led to conditions comparable to those of 1914–1918. Fortunately a quarter of a century of research since that war has led to a far better understanding of methods for control of tuberculosis. Countries fearing the ultimate outbreak of hostilities, through the tense years preceding their final advent, anticipated tuberculosis as a grave menace and prepared accordingly. Nevertheless, in spite of forewarning and preparation, a rise in the tuberculosis mortality rates appears already evident in the warring nations.

It seems worth while now to compare the tuberculosis history of the last war with what is known about tuberculosis in the present war, and to indicate what measures are being taken in this country to prevent a rise in the incidence of the disease. Modern war is total war. Whole populations, not detached armies, are engaged, through accelerated industry if not in actual combat, and under nation-wide food restrictions. The number of men under arms runs into millions in each of the warring powers. The armies themselves constitute large populations. In the succeeding pages the military and civil problems will be considered separately, but with recognition of the fact that the distinction is temporary and discharge of soldiers from active service and final demobilization will fuse the military and civil problems.

TUBERCULOSIS IN MILITARY SERVICE IN THE FIRST WORLD WAR

Epidemiologists and military surgeons in the United Ssates watched the course of tuberculosis in the early years of the first world war with uneasy anticipation. France's plight was made clear to America by the eminent public health official Hermann M. Biggs (6), who was sent to France in 1917 by the International Health Board of the Rockefeller Foundation. The French medical military service had returned 86,000 soldiers to civil life, with a diagnosis of active tuberculosis, within five months after the outbreak of war, and

by February, 1917 the reported number had risen to 150,000. It was said that exchanged prisoners of war afflicted with tuberculosis were also returning to France by thousands. Later considerable doubt was thrown on the accuracy of diagnosis in a large percentage of these cases, but the alarm spread by the initial reports forced tuberculosis upon the consciousness of public health authorities in all countries and particularly on the minds of army physicians in this country who were to be concerned later with the examination of large numbers of drafted troops.

Biggs himself insisted, as the United States began its own preparation for war, that stringent examination be made in order to exclude tuberculosis in recruits, stating his opinion that "any man with even a very limited amount of pulmonary tuberculosis that is latent or arrested is almost certain to break down under the strain of military training and army life."

Fortunately this view, which was held by many others, prevailed. A minority, following the old tradition of prescribing outdoor exercise for tuberculosis, opposed it. Fishberg (7) believed that military service was not more likely to activate dormant lesions than any civil occupation requiring muscular effort, and quoted Osler and other eminent clinicians in support of his opinion that soldiers with arrested tuberculosis could stand war's hardships well. A flood of articles on tuberculosis in soldiers were published in the succeeding months. Most authors vigorously opposed the views of Fishberg, and urged the rejection of prospective recruits with any evidence of tuberculosis or history of an active tuberculous lesion.

Shortly after the entrance of the United States in the war, at the request of the Council of National Defense, the National Tuberculosis Association, under the presidency of C. L. Minor (8), appointed an advisory committee on the military problems of tuberculosis. This committee, consisting of H. M. Biggs, G. M. Kober and C. J. Hatfield, outlined a program calling for recruiting examinations, reëxamination during service and treatment of cases discovered, and recommended that expert consultants be appointed throughout the country to pass upon the acceptance of prospective recruits referred by army physicians as possibly suffering from tuberculosis of disqualifying degree (Bushnell (9)).

The Surgeon General of the Army, General Gorgas, decided, however, on a far more ambitious plan, namely, to set up boards of expert examiners who would pass upon the state of the lungs of every man admitted to the Army. The administration of this mammoth task was entrusted to Colonel G. E. Bushnell of the Division of Internal Medicine of the Office of the Surgeon General, the Army's special expert on tuberculosis. Under his able direction numerous boards of experts drawn from civilian life were set up. Inasmuch as most of the members were themselves present or past victims of tuberculosis, special legislation was necessary to admit them to Army duty. Six hundred such examiners were ultimately obtained.

Regulations for the guidance of medical officers in examining for pulmonary tuberculosis, issued as Circular No. 20 of the Surgeon General's Office, provided instruction in elaborate detail. These were in large part still in force in August,

1940. Of this standard Bushnell (9) wrote: "It was undoubtedly of great benefit that a standard had been provided in Circular No. 20, upon which the examiner could rely and which relieved him of some of the burden of his responsibilities in the diagnosis of disputed cases. A standard, though imperfect, is believed to be an indispensable adjunct in Army tuberculosis work not only to support the examiner but also to secure the necessary uniformity of practice in the matter of discharge for tuberculosis." The regulations stressed physical examination by percussion and auscultation. Decisive significance was given to moist râles heard on inspiration after cough. In the hundreds of thousands of examinations to follow, this physical sign became the most important and often the sole criterion for rejection for tuberculosis. Bushnell himself called "the insistence upon moist râles as the only physical sign which justifies the diagnosis of activity" a "most radical position," but cited Piéry of France, Goldschneider of Germany and others in support of his stand.

Speed became a vital necessity in the examinations, as the soldiers streamed overseas. The Surgeon General's Office set 50 examinations per physician per day as the standard for the examining boards. Boards of ten physicians, however, commonly exceeded 1,000 examinations a day. One team of three examiners, working night and day in patriotic fervor, examined 1,763, 1,854 and 1,944 men respectively in three successive days!

Colonel Bushnell, a diligent student of tuberculosis problems, wrote voluminously in the American Review of Tuberculosis, the Journal of the American Medical Association and other periodicals. After the war he summarized the tuberculosis experience of the American Army for the comprehensive report of the Medical department of the United States Army in the World War (9). The data given in these pages are taken chiefly from that report.

The objectives, as given by Colonel Bushnell, were based on the grave need of the Army for rapid provision of man power. The situation was "unparalleled" and if mistakes were made in method "the exigencies of the war excused such a situation." The standards were set to provide objective data as the sole basis for rejection. The need for men was the primary consideration, although the subsequent possibility of heavy cost in pensions through induction of tuberculous soldiers was recognized. Bushnell gave his estimate, which he qualified as "conservative," that pensions might cost the government $1,000 per tuberculous soldier inducted. The sequel has borne him out that this estimate was indeed conservative.

Between 1917 and 1920 numerous articles were published in American medical journals dealing with the examination of recruits for tuberculosis in the United States and Canada. Pratt and Brown (10) and Matson (11) in the United States and Elliott (12) and Stewart (13) in Canada were among many who described their experience in excluding tuberculosis from the Army. There is nothing in their papers to indicate they felt the work was not well done. On the contrary, pride was frequently expressed over the way in which organization and skill appeared to function in eliminating tuberculosis as an Army problem. No premonition was apparent of the disappointment and criticism of later years.

The analyses of recent date lament the inadequacy of diagnosis, but there is more justification in implicating the organization which permitted induction in the Army prior, not subsequent to the examination which detected tuberculosis. The number of men found by physical examination to have tuberculosis and rejected as a result was large. Unfortunately from the point of view of future federal cost, rejection in the early stages of the war took place frequently in the mobilization camps after the recruits were technically in the Army. Official figures (14) indicate that 4,519 soldiers were rejected for pulmonary tuberculosis from the first million selectees at the mobilization camps and 5,576 from the second million men. The much larger number of 44,305 had already been rejected by local boards. Thus 54,400 men were rejected for pulmonary tuberculosis in obtaining approximately 2,000,000 soldiers. Astonishingly, tuberculosis of other organs was listed as a cause for rejection in the large number of 9,312 men, and in 17,119 tuberculosis of some type was suspected, entailing subsequent special consideration. A relatively small number of men with known tuberculosis, 1,231, were retained for limited service and rehabilitation. The total rate for rejection for tuberculosis, combining exclusion by local boards and camps, was given as 24.9 per 1,000 men.

In 1918 physical diagnosis was believed superior to roentgenography in the diagnosis of active tuberculosis. Bushnell (9) wrote: "Considerable pressure was exercised during the first months after the United States entered the war by a number of prominent physicians and radiologists to induce the Surgeon General to make the radiograph the decisive factor in the diagnosis of pulmonary tuberculosis."

The few studies made apparently failed to demonstrate the effectiveness of X-ray over physical examination. Bushnell referred to the work of Matson (11) who recorded the results of a special comparison of the two methods, writing: "Of 570 men rejected for clinically evident tuberculosis the roentgenologists recognized 54 per cent as tuberculous. In another group of 343 men, who, the roentgenologists stated, were unqualifiedly tuberculous and should be rejected on X-ray findings alone, irrespective of physical finding, only 315 were rejected after physical examination. The remaining 28 were considered either to be nontuberculous or to have obsolete lesions and were accepted for service. We have been able to follow these men through their military career and none has developed tuberculosis. Among another group of 1,500 men whom the roentgenologists diagnosed as very suspicious of tuberculosis, physical examination revealed only 128 cases of tuberculosis which were rejected. No cases of tuberculosis developed among the remaining 1,372 accepted for service." His conclusion was, "As compared with the physical examination, the roentgenological examination, even when done by an expert, occupies a place of secondary importance in the diagnosis of tuberculosis of clinical significance."

Thus a distinguished clinician wrote in 1920. As Spillman (15) later commented, the chest experts of those days were "not to be reproached for not having knowledge that came into existence only later, any more than the chief

of the army air service in 1917 is to be reproached because more efficient planes are available now than then."

Other reports were more favorable to X-ray examination. Lawrason Brown (16), relating the experience at Plattsburg and Camp Devens, stated that roentgenographic examination excluded 0.2 per cent more men than physical diagnosis and expressed the belief, based on the work of Cole, that two staffs could make satisfactory examination of 1,000 men a day at an expense of $1.00 per man.

However, graver faults than imperfection of diagnosis were responsible for some of the admission of tuberculous patients in 1917–1918. The idea was prevalent in some regions that exercise and change of climate were so beneficial that it might be wise to send patients into the Army for their health! Incredible as it may seem, certain units arriving at western mobilization camps for service were composed largely of sufferers from tuberculosis. In a group of 500 men from Texas arriving at Ft. McArthur, California, more than 100 were tuberculous, and five howitzer companies were said to include the majority of tuberculous patients from their particular part of the state (9).

It is pertinent in this place to point out that almost no fear existed of the transmission of tuberculosis from sick to well in camp. Exogenous infection was considered extremely unlikely in adults. Leading authorities hastened to reassure the public on this score. Fishberg stated that "the problem of tuberculous infection of soldiers need not be considered seriously." Bushnell (9) wrote, "The view was formerly held by all, and is still much too widely spread, that the population is divided as regards tuberculosis into a healthy majority and a tuberculous minority and that tuberculosis is infectious for adults, at least for those who are not already labeled tuberculous. . . . The elimination of the tuberculous from the Army in this view would be urgently required for the protection of their healthy comrades.

"What may be called the modern view is based upon the well-established fact that practically every civilized adult has come into contact with the tubercle bacillus and has thereby acquired what in a sense is a tuberculous infection. But in the large majority of the population this tuberculous infection remains latent throughout life and amounts to a vaccination against tuberculosis. And in those less successfully protected against tuberculosis the form of the disease which declares itself is chronic and often relatively benign, differing materially from the form of tuberculosis met in young children and others who have had no previous contact with the disease before acquiring an infection with massive dosage. An individual already infected with tuberculosis can be reinfected from without if at all, only by large amounts of tuberculosis virus. If thus capable of exogenous infection he is likewise subject to endogenous reinfection, or will be unable to prevent the extension of already existing, but perhaps latent, tuberculous processes within his body. Exogenous infection in civilized man is not, therefore, of importance."

Occasionally a different view was expressed cautiously. In an editorial (17) in

the Journal of the American Medical Association on war measures against tuberculosis, reference was made to recrudescence from latent tuberculous lesions under conditions of strain, but the statement was made that "the theory that infection is always obtained in early life has not been conclusively proved." The editorial was based on a preceding publication by Theobald Smith.

The number of men actually rejected by special tuberculosis examiners in both primary and reëxaminations of recruited soldiers and incoming drafted men was given by Bushnell (9) as 22,596 out of 3,288,669 examined. The discharge rate was 0.687 per cent. Six hundred and thirteen men were discharged with a diagnosis of nonpulmonary tuberculosis and 1,461 with supposedly arrested tuberculosis were held for limited service. After November, 1918 the examining boards were engaged in demobilization. The number of cases of tuberculosis found was described by Bushnell as "gratifyingly small," namely, 542 per million men examined. In his opinion this and the supposedly low rate of breakdown in France rewarded the organization for the care taken in the exclusion of tuberculosis from the troops. He recorded that 2,240 men in the Army died of tuberculosis between the beginning of the war and January 1, 1920. During this period serious attention had been given to the tuberculosis problem in the American Expeditionary Force in France. The early months of the war demonstrated the need of a special army tuberculosis organization in France to standardize diagnosis and establish facilities for care. In March, 1918 G. B. Webb was sent to France to accomplish these purposes.

After the early 1920's the gravity of the tuberculosis legacy from the war became evident. Figures obtained from the Budget Officer of the Veterans Administration through the courtesy of Dr. Martin J. Cooley and published elsewhere (18) summarize the tuberculosis problem in veterans from the point of view of number of men involved and cost:

"The records of the Veterans Administration show that, in 1921, 25,603 World War veterans with tuberculosis were admitted to hospitals under the jurisdiction of the administration. In 1940, 9,039 World War veterans were admitted. The total number of tuberculous veterans hospitalized in veterans' hospitals varied from a peak of 44,591 in 1922 to a low figure of 13,615 in 1934 and the somewhat higher figure of 16,411 in 1940. The annual cost of hospitalization varied from a maximum of $29,751,114 in 1922 to $9,552,647 in 1940. The total cost for the twenty years from 1921 to 1940 inclusive was $348,701,662. The figures are for veterans of all wars, but the Veterans Administration estimated that 95 per cent of the cost was for World War veterans. Finally, in 1940, 54,855 World War veterans judged to have service connected tuberculosis were on the rolls of the Veterans Administration receiving compensation or pensions, which in that year were estimated to amount to $35,490,848. Spillman (15), from a study of annual federal reports, estimated that up to October, 1940 tuberculosis in veterans of the World War had cost approximately $960,000,000 in compensation, vocational training, insurance and hospitalization.

"In analyzing such costs it must be recognized that not all of the expense would have been saved had tuberculosis been completely excluded from the

Army. Many of the soldiers found to have tuberculosis would have been treated at public expense in the course of time in municipal, county or state institutions, at a cost comparable to that in the federally operated hospitals. However, exclusion would have reduced the heavy costs for insurance and compensation in the thousands of cases in which tuberculosis in the absence of preinduction detection was adjudged 'service connected'."

It must be recognized that the figures given do not present a true picture of the tuberculosis problem actually resulting from the war. Repeated liberalization of the term "service connected" obligated the hospitals of the Veterans Bureau to accept a large number of cases in which tuberculosis developed long after demobilization. There is little medical justification for considering all of these actually due to the strain of military service in 1917–1918.

A point that should be considered before closing the subject of the breakdown of American troops is poison gas. Early reports suggested that gas might have lighted up some of the tuberculous lesions observed. Later this view was generally abandoned. Four years of observation of gassed men after the war convinced Cole (19) that "war gassing has little to do with the development of pulmonary tuberculosis."

TUBERCULOSIS IN MILITARY SERVICE IN THE SECOND WORLD WAR

With the lessons of the first world war at hand the defects inherent in the system then followed in the mobilization of troops should now be avoided. In the intervening years diagnosis of tuberculosis has improved greatly and there is no longer any question about the superiority of roentgenographic as compared with physical examination. The Surgeon General of the Army clearly recognized X-ray examination of recruits as desirable long before actual hostilities, and it was regularly used in the admission of officers and other selected personnel.

In May, 1940 when the need for defensive mobilization was already apparent, the surgeons general of the military services called upon the National Research Council for technical advice in accordance with the established purposes of the Council as a scientific body functioning primarily in national emergency. In the succeeding months a large number of advisory committees were set up in the Division of Medical Sciences for various medical specialties (20). One of these, a committee on tuberculosis, organized as a subcommittee of the Committee on Medicine of the Division, was requested to aid the Surgeon General of the Army in the revision of that part of Mobilization Regulations dealing with the examination of the chest in recruits. This committee consisted of J. B. Amberson, B. H. Douglas, H. R. Edwards, E. R. Long, P. P. McCain and J. J. Waring. The majority of the recommendations of this committee were incorporated in a new issue of Mobilization Regulations on August 31, 1940. The committee urged that X-ray films be made mandatory in the chest examination of men registering under the Selective Service Act, but it was not possible to incorporate this as a requirement in the standards of that date. Roentgenographic equipment could not be made available immediately in the majority of the induction centres, and this fact and other administrative procedures over which the Surgeon General did

not have control prevented universal roentgenographing. On his recommendation a directive was issued on October 25, 1940, by The Adjutant General of the Surgeon General, requiring that chest X-ray examination be made on all registrants in cases where pulmonary disease was suspected and making chest X-ray examination routine in all cases where local X-ray facilities made it possible.

In the rapid mobilization which began in the fall of 1940 only three of the nine corps areas X-rayed all of the men inducted. In the other corps areas X-ray examination ranged from a majority of the men certified by the local boards in the seventh corps area to almost complete omission of X-ray examination in other corps areas. Equipment was gradually made available in all areas and by March 1, 1941, 51 per cent of the men called to the induction centres had received roentgen ray examination.[4]

During the succeeding months equipment was steadily distributed to the induction centres and on June 3, 1941, The Adjutant General issued the following order: "In view of the great importance of chest X-ray examinations in the exclusion of individuals with pulmonary tuberculosis and other significant intrathoracic defects from the military service, it is directed that provision be made without delay for the inclusion of chest X-rays in the examination of all registrants appearing before induction boards."

Provision has been made also, in War Department Circular No. 146, issued July 22, 1941, for inclusion of X-ray examination of the chest in the terminal physical examination of officers, reserve nurses, warrant officers and enlisted men discharged from active service.

Recently (January 22, 1942) recommendation from the Surgeon General's Office to The Adjutant General has been made to amend previous action so that all applicants for voluntary enlistment and reënlistment in the Regular Army and the National Guard, with the exception of soldiers applying for reënlistment within ninety days after discharge from prior military service, will have chest roentgenograms.

On January 1, 1942, a system of single examination of selectees by Army examining boards was adopted, replacing the previous dual examination by local boards and medical boards at the induction centres. It is believed that the two recent orders to which reference has been made will enable X-ray examination of practically all men entering the Army after the first part of 1942. On February 1, 1942, the Army was making or had made extensive use of standard size celluloid X-ray films, paper X-ray "films" and 4 by 5 inch stereo-photoroentgenograms.

The first standards drawn by the Office of the Surgeon General on the basis of recommendations by the Committee on Tuberculosis of the National Research Council proved open to certain objections in actual practice and were revised by the Office after further extensive consideration by the committee in the spring of

[4] For the information here given on recent and current operation of the induction examinations I am indebted to Brig. Gen. C. C. Hillman of the Office of The Surgeon General of the War Department, who has been continuously helpful to civilian bodies endeavoring to coöperate in the medical problems of national defense.

1941. The improved standards require X-ray examination before acceptance of men selected for service. Men with evidence of pulmonary tuberculosis are to be rejected, except when the lesions are of such character that no fear of reactivation is warranted. Specifically the standards limit acceptance in this respect to men with no more serious change than small fibroid lesions represented in roentgenograms as sharply demarcated strand-like or well defined nodular shadows not exceeding a total of 5 sq. cm. in standard size films, and even in such cases require deferment until a second film examination has proved such lesions stable. Calcified lesions bar men from acceptance only when they are large and multiple. The limits in size and number have been set down in the rules in deference to a proved need for an objective, readily interpreted standard, with full recognition of the fact that exact definition in this respect is arbitrary.

From all available evidence it appears that the rejection rate for tuberculosis in the men reaching the induction boards has been between 0.5 and 1.5 per cent. Ashbury (21) reported 1.2 per cent rejections in 11,870 men X-rayed in Baltimore. Plunkett (22) reported 0.9 per cent in three large cities in upper New York State and Edwards and Ehrlich (23) 1.14 per cent for New York City. These figures are for rejections by induction boards; that is, they do not include the previous rejections by local boards. Figures released by the National Headquarters of the Selective Service System (24), based on 19,923 representative samplings by states prior to May 31, 1941, indicate a total rejection rate of 1.4 per cent for active pulmonary tuberculosis and an additional rejection rate totalling more than this for suspected pulmonary tuberculosis and nonpulmonary tuberculosis. Reynolds (25) has given the figure of 0.63 per cent rejection by the local boards and 1.83 per cent rejection by the induction boards in Pennsylvania. Canny (26) has recently summarized recent incomplete data from other sources.

On the basis of the percentage of rejection of 0.5 to 1.5 in areas where roentgenography was practiced, and his estimate that 1,000,000 men were inducted into the Army without X-ray examination in other areas, Mercer (27) has calculated that between 5,000 and 15,000 persons with tuberculosis have been taken into the Army. He urges immediate roentgenography of men who entered unexamined by X-ray in order to detect these. Fortunately, it appears that relatively few actual breakdowns from tuberculosis have occurred in the Army in recent months. Data available to the Army for the first six months of 1941 show an admission rate of 0.85 men per 1,000, a rate lower than that prevalent before the Army was expanded in current mobilization (28).

The disposition of the cases discovered through the several agencies, that is, the local boards, the induction boards and the medical corps of the Army after induction, is a problem of urgent importance in public health. The majority of cases discovered after induction will follow the normal course of referral to the Veterans Bureau. The others, rejected before induction, should receive immediate attention in private medical practice or through county and state public health services. Several systems in which counties, states and local tuberculosis societies participate are in operation, and there is a growing tendency toward uniformity of practice. Pollock (60), in commenting on the great opportunity

inherent in the mobilization mass survey now under way, has estimated that 88,000 cases of tuberculosis will be detected in six million men called up, and that their care, aside from pensions in men actually inducted, will cost approximately $42,000,000. Ultimate costs will depend on the future value of the currency, but all are agreed that the present case-finding campaign, necessitated by mobilization, presents an opportunity for early detection of many cases and prompt institution of suitable care.

TUBERCULOSIS IN CIVILIAN POPULATIONS IN THE FIRST WORLD WAR

Reference was made in the opening paragraphs of this paper to the rapid and serious increase in tuberculosis in Europe between 1914 and 1918. In 1920 Frankel (29), a recognized statistical expert, believed the war had undone all the favorable effects of the previous thirty years of public health work. As it turned out this view was unduly pessimistic, for rapid recovery occurred in most countries within a few years.

Early in the course of our participation in the war the tuberculosis problem of Europe excited sympathy in the United States. In 1917 the Rockefeller Foundation sent a commission under the direction of Livingston Farrand to France to aid in the control of tuberculosis, and the Red Cross sent similar commissions to France and Italy under the direction of Wm. Charles White. These commissions organized dispensaries for the control of tuberculosis on an extensive scale, helped the local officials in innumerable ways and brought back much useful information to the United States. J. A. Miller (30), a member of the Rockefeller commission to France, furnished an analysis of the rise in tuberculosis in five European countries, France, England, Belgium, Germany and Austria-Hungary, which has unusual value for its bearing on the present situation. In France and England the chief rise in tuberculosis rates was in young women, and since neither country suffered seriously from undernourishment and both called heavily upon young women for industrial service, the increase was attributed to the strain of increased labor. In contrast, the other three countries suffered gravely from malnutrition and their far more serious rise in tuberculosis was credited chiefly to the latter factor. A similar relationship between industry and tuberculosis was observed in other countries, including neutral lands like Holland, in which industry was stimulated much as in the nations at war.

Analysis of the course of tuberculosis during and after the war in central Europe shows clearly the influence of unfavorable environment on endemic tuberculosis. Wolff (31) called the war and privations of the period an "involuntary mass experiment of more epidemiological significance than endless theorizing on the pathology of tuberculosis."

The problem in Germany was subjected to repeated scientific inquiry. Most of the factors cited in the different countries as contributing to the increase in tuberculosis operated in unison there. Emerson (32) described Germany as an illustration of acute epidemic spread of tuberculosis due to uncontrollable unsanitary conditions of housing, lack of means to separate the sick and the well and the long continued shortage of food. An early study

after the war was made by Bruns, an officer with the American army of occupation. Bruns (33) voiced the generally accepted view that privation undermined resistance, permitting infections that would ordinarily be well controlled to progress to active and fatal disease. Tuberculosis more than any other disease, he wrote, must be controlled from the standpoint of resistance. He emphasized malnutrition as the chief debilitating factor in Germany, stating that the adult dietary intake sank from a daily average of 3,000 calories, with 12 per cent protein, 20 per cent fat and 68 per cent carbohydrate, before the war, to 1,400 calories, with 8 per cent protein, 9 per cent fat and 83 per cent carbohydrate at the end of the conflict.

Exhaustive analyses appeared in the German medical press. The declining tuberculosis rate of the years preceding the war was generally interpreted as the result of two factors, improved nutrition and a mild but universal tuberculization of the race commencing in childhood with small infecting doses and immunizing against the superinfections of later years, whether exogenous or endogenous (34). This view was dominant in the United States also. Allen Krause (35), always a leader in American thought, wrote, "Perhaps our most important practical task is, for the time being, at least, to accept infection as part and parcel of the normal make-up of man and lay emphasis on preventing morbidity."

An elaborate analysis of the German rise in tuberculosis was made in 1921 by Kirchner (3). He blamed malnutrition chiefly for the evil, naming the excessive labor of women in industry and crowding and poor heating in houses as contributory factors. The crisis was precipitated, according to his analysis, by the failure of the wheat and potato crops late in 1916. Up to that time the ration per capita had averaged almost 2,000 calories per day with 54 g. of protein; by June, 1917 it had been reduced to 1,100 calories with 30 g. of protein. It was at this time that "war oedema" began to develop in the most underpriviliged.

Various authors referred to change in type of tuberculosis, with a tendency to assume a more generalized form. For example, Drügg (36), a surgeon, described an increase of 200 per cent in the incidence of tuberculosis of the lymph nodes in a surgical clinic in Cologne.

Germany made a prompt but temporary recovery immediately after the war. The tuberculosis mortality rate in Prussia dropped from 230 in 1918 to 135 in 1921. But with the economic catastrophe of 1922 and 1923 the mortality rose again, reaching a recorded rate of 153 in 1923. In this connection Wolff (31) stressed the "closeness with which the mortality figure reacts to unfavorable environment."

In Austria conditions differed only in that the tuberculosis rate was high at the beginning of the war, the increase was greater and recovery more gradual. In 1914 the mortality from tuberculosis in Vienna was recorded as 278 per 100,000, in 1918 as 427, in 1919 as 490 and in 1920 as 405. Again malnutrition was considered the chief deleterious factor. The Austrian government issued a statement incriminating this rather than other environmental factors (37).

In the large cities of Serbia, scene of continuous fighting and indescribable privation, the rise in the tuberculosis rate was appalling. The recorded rate for

Belgrade was given in Knopf's (38) review of the European tuberculosis problem as 1,483 per 100,000 population in 1917.

A report from Poland emphasizes the differential effect on age segments of the population. The mortality rate for Warsaw, already high before the war, tripled during the German occupation. According to Kopec (39) in 1918–1919 tuberculosis accounted for a quarter of all deaths and the ravages were worst in adolescent children.

As may be seen from the foregoing pages, malnutrition was considered the major factor in the tuberculosis epidemic of Central Europe by investigators writing during or immediately after the war. It is significant that a reëvaluation of the several factors could be made later in the light of subsequent knowledge. In 1930, twelve years after the close of the war, years characterized by phenomenal growth in the science of nutrition, Schroeder (40) reviewed the German epidemic. His analysis convinced him that the nutritional factor was the basis for the tuberculosis rise and that insufficiency of protein was chiefly responsible. His observations indicated that when the protein level was reduced below 80 g. per day the good progress of tuberculous patients in hospitals ceased. During this period, he claimed, there was no vitamin deficiency, fresh fruits and vegetables being available throughout the war. The favorable normal protein effect, in his opinion, was due to its specific dynamic action. All of his studies had convinced him that a high metabolic level is important in resistance to tuberculosis.

A confirmatory view was expressed by Faber (41) in 1938, twenty years after the war. His analysis has the special merit of coming from a country in which it was more nearly possible to separate the factors which might contribute to a rise in tuberculosis mortality than was the case in the warring countries. Denmark shared in the tuberculosis increase. Its rate, according to Faber, was 135 in 1913 and 176 in 1917. As in other countries, the proportionate rise in tuberculosis mortality was greater than the rise in general mortality. Also there was a tendency toward increase in the generalized forms of the disease. Denmark exported food to England and Germany until the submarine blockade of 1917. During this time prices soared and food difficulties for the Danish people were great. Amounts of meat and fish consumed were especially low, although the caloric total remained about as before. With the advent of the blockade Denmark retained much of her meat produce and at the same time introduced a rationing system ensuring more adequate distribution of food throughout the population. In the year following, definitely prior to the drop in other European countries, tuberculosis fell rapidly. Subsequently a housing shortage developed, presumably increasing exposure to tuberculosis, a factor considered of epidemiological importance in other countries, where it was coincident with malnutrition. The improvement in tuberculosis mortality in Denmark appeared unaffected by the housing shortage. Faber accordingly concluded that protein deficiency was the major factor in the tuberculosis rise.

Faber stated also that the rise and fall of tuberculosis mortality appeared to be independent of the influenza epidemic of 1917–1918. The possible effect of this is perhaps best studied in the United States, which, although a warring country,

suffered far less seriously than Europe from nutritional impoverization and increased urbanization and crowding. The United States, like other countries, experienced a rise in its recorded tuberculosis rate in 1918. The rise accompanied an increase in general mortality, due to influenza. There was extended discussion as to the relation of the two. Fishberg (42) adopted the view that influenza had little effect on the course of tuberculosis. This concept was attacked by many, and especially sharply by Minor (43), who claimed the irritative effect of influenza on dormant tuberculous lesions was disastrous. Other writers had already referred to influenza as an incitant of tuberculosis in the Army. Stewart (44), whose experience in the Canadian army convinced him that soldiers with arrested tuberculosis stood ordinary military hardships well, felt that such increased incidence in soldiers as did occur in war time could be attributed to the severe recurrent epidemics of acute respiratory disease. As he said, "the whole army coughed," and in some soldiers old tuberculous processes were lighted up. Amberson and Peters (45), in a conservative evaluation, concluded that to a varying degree influenza *might* reactivate quiescent lesions.

An analysis by Krause (46) appears sound. He considered the recorded rise in tuberculosis largely fictitious, because it occurred chiefly in the actual months when the epidemic of influenza was at its height. In New York State in October, 1918 tuberculosis mortality was 50 per cent higher than the expected rate for that month. It was at this very time that influenza struck the state most violently. In Krause's opinion it was "quite likely that every one of the 'excess' tuberculosis deaths during October, 1918 was due to influenza in a tuberculosis patient." He believed also, in view of the notable drop in the tuberculosis mortality during the following year, that the influenza epidemic removed a large number of patients with advanced tuberculosis who would have succumbed to the latter disease in 1919.

As the years passed there has been rather general concurrence in this opinion. It is significant to recall, however, that the influenza epidemic of 1918 was itself a product of the war. Thus the recorded rise in tuberculosis mortality in the United States in 1918, whether truly representing tuberculosis mortality or not, is to be charged to the war.

TUBERCULOSIS IN CIVILIAN POPULATIONS IN THE SECOND WORLD WAR

At the date of writing this article it is too early to determine what has been the effect of the conflict on tuberculosis in the warring countries. From the fragmentary data available it appears that a rise in tuberculosis mortality has commenced, at least in the British Isles. In a letter (47) to the Journal of the American Medical Association dated June 21, 1941, the position of England as respects tuberculosis was described as satisfactory, but a later message (48) to the Journal from its London correspondent, dated November 29, 1941, referred to tuberculosis as the single exception in a satisfactory public health situation. The ministry of health reported a rise of 9.7 per cent in the mortality from tuberculosis in 1939 and 1940, the increment being greatest in young women. Selective mortality in women was strongly reminiscent of the last war.

The correspondent quoted Sir Ernest Graham-White as suggesting a relation with nutrition.

Drolet (49) has made a survey of recent reports and written as follows: "From England, Wales and Scotland certain preliminary reports have been issued. In England and Wales, the deaths from tuberculosis in 1939 are reported to have totaled 25,624; in 1940, 28,144. For 1941, data for the first six months only are at hand, but comparing the first half of 1939, 1940 and 1941 the figures run as follows: 14,131; 15,779; 16,377.

"Brief reports from the County Medical Officer of Health of London give the tuberculosis death rate per 100,000 population in England and Wales, in 1939, as 64 and, in 1940, as 70. For London itself there is a higher level and a greater increase; in 1939, the rate is figured at 78 and, in 1940, at 97.

"From Scotland have come indications of a material rise in tuberculosis. First, for the country as a whole in 1939, the deaths are stated to have been 3,526; and, in 1940, 4,003. For the first half of 1941, they numbered exactly 2,300, which would tend to indicate for the year as a whole a still higher figure than in 1940."

There is no question that, in the light of the experience in Germany in the first world war, nutrition is under constant consideration in all countries as a factor concerned with tuberculosis. England has undergone serious privation, but national nutrition is well organized. The London correspondent of the American Medical Association (50) on December 13, 1941 made a favorable report summarizing with the statement, "We are not getting such food as we should like but what is sufficient for maintaining health and capacity for work."

In October, 1941, at the meeting of the American Public Association, Sir Wilson Jameson (51), Chief Medical Officer of the Ministry of Health of London, described a system of rationing and priorities designed to furnish food according to greatest need. A survey of 103 workers' families in London in the spring of 1941 indicated that the members were receiving from 1,740 to 2,750 calories with 50 to 80 g. of protein, 60 to 105 g. of fat and 250 to 350 g. of carbohydrate. He stated that thus far there was no evidence of serious malnutrition, but added, "the margin of safety we possess must be very small." Jameson also referred to an increase in tuberculosis in females between fifteen and twenty-five years, without committing himself as to its cause.

Laidlaw and Macfarlane (52) have reported an increase in tuberculosis in Glasgow, which they attributed to long hours of work, general strain and ill spent leisure. Undernourishment was named as one contributing factor.

That malnutrition is rife in certain portions of the continent is perfectly clear from gathering records. Whether or not it is accompanied by a rise in the tuberculosis rates is not yet evident. The correspondent of the Journal of the American Medical Association (53) in Belgium a year ago (letter of May 2, 1941) described food shortage as a pressing problem. In spite of a system of rationing designed for optimum distribution, protein deficiency was serious. Pregnant women were receiving only 35 g. daily, in a diet 800 calories short of the accepted

need, and deficiency oedema had already been observed in some parts of the population.

At the fall meeting of the Milbank Memorial Fund reports were presented by various investigators who had made recent studies of nutrition in Europe. The reports were summarized by Boudreau (54). Sawyer and Stokes in separate descriptions of their experiences agreed that the most severe food shortage in Europe in the early part of 1941 was in Spain, where the daily caloric average was estimated at 800 to 900 calories for adults. Physical signs of malnutrition were evident in the Spanish population. Stokes stated that meat stocks in unoccupied France were very low and a shortage was impending in potatoes, vegetables and sugar. There was great insufficiency in fats and in general the national diet was deficient in vitamin A and the B-complex. Stokes also presented comparative data on the daily ration in six European countries as learned from sample ration cards. Denmark, Italy and Germany appeared to be better off than Belgium, Holland and France. The French population was believed to be living on an average daily intake of 1,400 to 1,500 calories, although in some parts it might be close to 1,100. Unoccupied France was described as in a worse nutritional state than occupied France. Detailed information on the ration has been given in a letter of December 1, 1941 to the Journal of the American Medical Association (55) from its Paris correspondent.

A somewhat more optimistic report on nutrition in France has been published by Youmans (56), based on personal observations made between February and June, 1941 in the course of a survey sponsored by the International Health Division of the Rockefeller Foundation. Tests of samples of the population in the Marseilles area and on a smaller scale in the Paris area were made by standard methods. Moderate protein deficiency was noted in the population over but not in that under nineteen years of age. Moderate deficiency in vitamin-A concentration in the body was seen in all age groups. Vitamin-C deficiency was evident to slight extent by physical examination, to greater degree by blood study and not apparent by skeletal roentgenography. There was little or no actual scurvy. Mild anaemia was seen in certain age groups. In general, nutritional deficiency was not grossly evident and could be detected only by suitable laboratory tests, but Youmans felt that we might now be seeing the beginning of a deficiency that may become serious with long continuation of present conditions.

In Greece and the Balkan States according to current newspaper accounts there is wide-spread famine. Official figures as respects tuberculosis are not available.

In the United States precautions are being taken against nutritional deficiency in the light of the most modern scientific knowledge. In connection with the preparedness program the Committee on Food and Nutrition of the National Research Council has published a table of recommended daily allowances for specific nutrients (57). This specifies a daily intake of 2,500 to 3,000 calories for a man of 70 kg. weight, the number within that range varying according to his

degree of activity, and 2,100 to 2,500 calories for a woman of 56 kg. The protein requirement for an active man is given as 70 g. and for a woman 60 g. Other standards that may be significant in tuberculosis are as follows, for either sex: calcium, 0.8 g.; iron, 12 mg.; vitamin A, 5,000 international units and ascorbic acid, 75 mg. Sebrell (58) wrote, "we do have enough information for practical use in developing an adequate nutrition program. The urgent problem is to get every health department in the country to include nutrition as an important part of its activities."

Nutrition has been considered at length in this review because it is almost universally believed to have important bearing on the problem of resistance to tuberculosis. There is no question that throughout the world national programs take nutrition into account in this connection, as well as in its more general relations. It is also evident that the United States is in an advantageous position at present.

However, lowering of resistance through malnutrition and other adverse factors, serious as it is, may not be the gravest predisposing factor in a rise of tuberculosis under present war conditions. The acceleration of industry, leading to crowded quarters in industrial districts, favors exogenous infection, which was discounted as a menace in the other war. Even if superinfection in adults were impossible, a premise quite contrary to current opinion, it must be recognized that a much larger porportion of the urban population is uninfected at the present time than twenty-five years ago, and by all admittedly susceptible to exogenous infection. The exigencies of war have created other opportunities for wide spread of infection than those contingent upon industrial crowding. The mass migrations and evacuations have created huge refugee problems. A specific danger has arisen in the evacuation of tuberculosis sanatoria in European countries to make room for war and air raid casualties. The Council of the National Association for the Prevention of Tuberculosis has protested that this is a very unwise measure, already (1939) exposing the population (59). Although analyses are not yet available the air raid shelters may be promoting a spread in tuberculous infection.

It is evident that a grave menace exists of another world wide recrudescence of tuberculosis. Its prevention will require vigorous effort against the spread of infection and all measures possible to maintain a high level of resistance to disease.

CONCLUSIONS

Tuberculosis increases in seriousness in war time. The problem must be considered in both its military and civil aspects.

In the world war of 1914–1918, large numbers of tuberculous soldiers were discharged from the various armies, most of whom were believed, in the light of subsequent examination, to have had latent lesions on admission. The methods of physical examination of recruits employed at that time, which made but negligible use of roentgenography, were not adequate to detect this type of tuberculosis. The United States has carried a heavy financial burden for maintenance

and pensions for tuberculous world war veterans since 1918. Much of this, however, is not attributable to the war from the medical point of view, but rather to administrative definition of the term "service connected."

In the present world war increasing effort is being made in the United States to avoid induction of soldiers with tuberculosis. Measures ensuring X-ray examination of practically all recruits admitted to the armed forces are in effect. In the fifteen months of mobilization prior to January 1, 1942, however, large numbers of troops were admitted without X-ray observation. These should be examined by this method promptly and any men with significant tuberculosis discharged. About 1 per cent of men selected by local boards and sent to induction centres have been found to have tuberculosis of sufficient significance to warrant their rejection. The local boards themselves have discharged a similar number on the basis of previously existent evidence of tuberculosis.

In the first world war it was believed that exogenous tuberculous infection was not to be feared, since at that time all healthy adults were already thought to carry latent lesions, and the advent of illness was attributed to breakdown under strain. Currently, there is reason to believe that many non-infected persons are inducted, and that exogenous infection is significant for both infected and non-infected persons.

During and after the first world war a great increase in tuberculosis occurred throughout Europe. Several factors appeared to share in its production. In the countries least seriously affected, the acceleration of industry, with longer hours, crowding and greater exposure, may have been entirely responsible. In central and eastern Europe these factors applied and, in still greater measure, the factor of profound malnutrition. Protein deficiency was implicated especially.

Influenza affected the reported tuberculosis mortality rate during the first world war. The excess deaths may have represented fatal influenza in tuberculous patients rather than tuberculosis aggravated by this disease.

Tuberculosis already appears on the increase in the warring nations in the second world conflict. No single cause is apparent. All the factors concerned in the other world war again operate. Malnutrition is known to be serious in certain countries.

Active measures to prevent the spread of infection and continuous consideration of the maintenance of resistance to disease are vital in the prevention of another wide-spread recrudescence of tuberculosis.

CONCLUSIONES

La tuberculosis acrecienta en gravedad en épocas de guerra, y el problema tiene que ser considerado tanto en sus fases militares como civiles.

En la guerra mundial de 1914–1918, se dió de alta de los varios ejércitos a grandes números de soldados tuberculosos, en la mayor parte de los cuales se consideró, a la luz de los exámenes subsecuentes, que ya había lesiones latentes a su ingreso. Los métodos de examen físico de los reclutas empleados en aquella época, que utilizaban en forma menospreciable la roentgenografía, no eran adecuados para distinguir la tuberculosis de ese tipo. Desde 1918 los Estados

Unidos han tenido que sobrellevar un pesado gravamen económico en lo tocante a mantenimiento y pensiones para los veteranos tuberculosos, pero gran parte de esto no puede ser imputado a la guerra desde el punto de vista médico, sino más bien a la definición administrativa del término "relacionado con el servicio."

En la guerra actual se están haciendo esfuerzos más cuidadosos en Estados Unidos para evitar el ingreso de soldados tuberculosos, habiéndose puesto en efecto providencias relativas al examen roentgenológico de casi todos los reclutas recibidos en las fuerzas armadas. Sin embargo, en los quince meses de movilización anteriores al 1° de enero de 1942, se admitió a un número crecido de soldados sin observación roentgenológica, por lo cual debería examinárseles sin tardanza con ese método para dar de alta a todos aquéllos en que haya lesiones tuberculosas de importancia. Aproximadamente en 1 por ciento de los individuos escogidos por las juntas locales y remitidos a los centros de ingreso se descubrió después tuberculosis de suficiente importancia para justificar su alta. Las juntas locales mismas han dado de alta a una proporción semejante, tomando por base signos tuberculosos previamente existentes.

En la primera guerra mundial creíase que no había que temer la infección tuberculosa exógena, puesto que por entonces considerábase que todos los adultos sanos ya tenían lesiones latentes, y la aparición de la enfermedad se atribuía a las consecuencias del esfuerzo sobrepuesto. Hoy día hay motivos para creer que se están recibiendo muchas personas no infectadas, y que la infección exógena reviste importancia tanto para las infectadas como las no infectadas.

Durante la primera guerra mundial y después de ésta, observóse un gran aumento en la tuberculosis en todas partes de Europa, participando aparentemente varios factores en ello. En los países menos afectados, la causa tal vez procediera en absoluto de la aceleración de la industria, acompañada de horas más largas, hacinamiento y mayor exposición. Así sucedió en el centro y oriente de Europa, sobreponiéndose a ello todavía en grado mayor, el factor de una desnutrición intensa, sobre todo en cuanto a falta de proteína.

La influenza afectó la mortalidad tuberculosa comunicada durante la primera guerra mundial, y el exceso de muertes tal vez representara influenza letal en tuberculosos, más bien que tuberculosis agravada por dicha enfermedad.

La tuberculosis ya parece ir en aumento en los países que participan en el segundo conflicto mundial. No hay ninguna causa aislada aparente, y de nuevo intervienen todos los factores que actuaron en la otra guerra mundial, sabiéndose ya que la desnutrición es grave en ciertos países.

En la profilaxia de otra recrudescencia generalizada de la tuberculosis, es de vital importancia iniciar medidas activas que impidan la propagación de la infección, y considerar continuamente el mantenimiento y resistencia al mal.

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CHANGING SCENES IN TUBERCULOSIS

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Extraordinary developments in medicine have occurred during the past generation and perhaps in no field have they been more marked than in that of tuberculosis.

Inasmuch as Allen Krause was prominently identified with the progress which these changes denote, it appears proper to review them briefly in this symposium which is a commemoration of Doctor Krause's notable contributions to tuberculosis.

We may conveniently begin with the turn of the century.

In 1900 the death rate from tuberculosis in the United States was 200 per 100,000 of population and in New York City it was 300. In 1940 the rates were 46 and 54 respectively.

In 1900 there were only 4,485 beds in 19 different institutions in the United States. In 1938 there were 98,801 beds in 1,140 institutions.

These two sets of statistics are closely interrelated, for there is no doubt that one of the most potent factors in the diminution in the incidence of tuberculosis has been the elimination of the dangers of household infection by means of institutional segregation. The great impetus for the wide-spread hospitalization movement in this country was furnished by the Washington International Tuberculosis Congress in 1908.

During this period under consideration, education of the profession and of the public in the problems of tuberculosis became general and the conditions predisposing to infection in housing and industrial environment became better understood and led to great reforms. The National Tuberculosis Association, organized in 1904, with its numerous subsidiaries, has been a potent factor in this propaganda effort and the public health authorities gradually have taken over the main responsibility of the inauguration and enforcement of sanitary measures of control and of education which are now almost universal.

The danger from bovine infection was recognized and has now been practically eliminated through cattle inspection and the pasteurization of milk.

That tuberculosis was predominantly a disease of the poor was generally appreciated and that this involved factors of resistance as well as greater opportunities for infection was recognized and led to the great social movement for the elimination of such untoward conditions as undernutrition, overwork and other strains, insanitary housing and the like, to which the poor were especially exposed.

This movement, though guided by physicians, has enlisted the united efforts of social workers, public health nurses and thousands of enlightened non-professional groups into a crusade, as the antituberculosis campaign has been so aptly designated.

[1] 133 East 64th Street, New York City.

Upon the clinical side, physicians were chiefly concerned with the achievement of early diagnosis and of effective treatment.

Without belittling the importance of clinical symptoms or physical signs, it has now been conclusively demonstrated that the X-ray is the most valuable single method for early and exact diagnosis. Discovered in 1898 by Roentgen, the X-ray did not come into general clinical use for at least ten years, but is now recognized as indispensable in the examination of any suspected case of pulmonary tuberculosis and in recent years, through its utilization in so-called tuberculosis surveys of apparently healthy people, has been demonstrated as the *only* method by which the minimal lesions, which are the precursors of later disabling tuberculosis, can be detected. The technical side of roentgenography has been steadily improved and in recent years tomography and roentgencinematography have been notable advances in technique.

In treatment we have survived experiments with overfeeding and other special dietary fads, with climate as an essential factor, with various medicaments by mouth, by inhalation, by hypodermic or intravenous injection, both nonspecific and supposedly specific in nature, and have come back to *rest* as the fundamental basis of all treatment of active tuberculosis.

The principles underlying the value of rest, followed by a graduated return to active life under supervision, inculcated into the minds and practices of patient have been the great contribution of the sanatorium to the treatment of tuberculosis.

Closely associated in principle with rest, are the various forms of immobilization and collapse therapy in pulmonary tuberculosis. By immobilization tuberculo-toxins are less apt to be liberated into the lymph and blood streams and, by means of collapse, cavities and other active lesions are prevented from reinfecting new areas and their own healing by fibrosis is accelerated.

Artificial pneumothorax, phrenic interruption and the various forms of thoracoplasty all have their place here and together constitute one of the greatest advances of recent years in the treatment of pulmonary tuberculosis.

In the meantime, during this period scientific research into the underlying problems has been going on, although many of them are still unsolved.

One of the most valuable of these studies has been centered upon the complex problem of immunity. While it has been fairly definitely established that no complete immunity to tuberculosis exists in the human being or can be produced in animals, still a relative increased specific resistance is afforded by previous mild infections. Closely bound up with immunity are the manifestations of allergy.

This sensitization of human tissues by tubercle bacilli and their toxins as promulgated by Pirquet has been explored from many angles and has shed considerable light upon the epidemiology and the pathogenesis of tuberculosis. We know now that allergy is not immunity but is an invariable accompaniment of it, and some of the studies in this field have caused considerable discussion and differences of opinion as to the effect of a previous mild infection upon the development of subsequent active disease.

Practically, the question is raised as to whether valuable protection is thus afforded or whether it is to be our goal to preserve individuals as far as possible entirely uninfected. Scientific opinion is sharply divided, but there appears to be ample experimental and clinical evidence that the changed reaction in the body called allergy is accompanied by some specific resistance to new infection.

This has led to many efforts to immunize animals, and potentially human beings also, by protective inoculations. They have all been relative failures, from tuberculin to nonvirulent living bacilli, such as BCG. All efforts to obtain passive immunity by sera have completely failed.

One great practical advantage has resulted from our knowledge of specific allergy to tuberculous infection in the application of the tuberculin test. From it we know that while more than 90 per cent of all adults in urban population were infected thirty years ago, now the percentage is hardly more than 50 per cent and in many areas much lower. Our knowledge of the epidemiology of the disease has thus been considerably perfected, and the purification of the active principle of tuberculin and its standardization have been of great aid.

One of the issues that has indirectly developed from the study of immunity concerns pathogenesis and relates to the relative importance of endogenous and exogenous reinfection in the development of active disease. It is known that very few clinical cases of tuberculosis develop directly from the primary infection. It is a reinfection which produces the clinical disease. This reinfection is a new superinfection from the outside, that is, exogenous, or is a reinfection of new areas from the original infected area, often a long time latent.

Inasmuch as it is known that only a few bacilli can reach the lung alveolus and as a previous infection renders the production of a new focus of disease more difficult, it seems more likely that the reinfection disease should develop from the larger number of bacilli already present in existing lesions than from the few bacilli inhaled from an outside source of infection.

This has an important bearing upon the relative danger from exposure to infection in the two groups and the relative emphasis that should be placed upon an environment which would tend to prevent the latent lesions from breaking down and the strict avoidance of new exposure in the management of these cases. The case of physicians and nurses who can hardly avoid some exposure to infection is an important one in point. Of course, all agree that great and oft repeated infections may break down any such relative protection that may exist.

For many years experimental efforts have been expended to counteract tuberculosis in the body by chemical agents. These have uniformly failed.

The spectacular results obtained in other infections by the sulfonamide group of drugs have again directed attention away from the specific biological methods of approach to the chemical.

In recent months Hinshaw and Feldman have reported upon a sulfa-derivative called "promin" in some striking experiments with guinea pigs; 80 guinea pigs were inoculated with virulent tubercle bacilli. The controls all died of generalized tuberculosis. Of those treated with promin, ingested with their food, 60 per cent showed no evidence of tuberculosis when killed at the end of 192 days

and, in the remainder, only very slight evidence of tubercle, hardly recognizable grossly, was found.

These authors also experimented with this drug in human cases, but found that by mouth it produced a haemolytic anemia and, when administered parenterally, severe inflammatory reactions occurred.

While they warn against any undue optimism concerning the value of this drug in human tuberculosis, their animal experiments appear to have considerable significance and may point the way to important future developments. Certainly at present the emphasis of the immediate future in efforts to discover a specific cure for tuberculosis will probably be in the field of chemistry.

UNFINISHED BUSINESS

It is obvious from such a cursory review that the progress in our knowledge and in the control of tuberculosis has been astonishing.

It is, therefore, perhaps natural that there has developed a growing conviction in many quarters that this disease is practically conquered.

Without detracting in any way from the satisfaction which the past record affords, it might be wise to consider such claims as somewhat exaggerated and premature and to recognize that not only difficulties still lie ahead, but that there is still considerable unfinished business to be satisfactorily concluded before the ultimate goal of the antituberculosis campaign is reached.

This unfinished business falls into two categories: first, those involving the further prosecution and perfection of methods now employed and, second, those which involve the acquisition of new knowledge and such modification of our present methods which such knowledge would demand.

Problems Involving the Perfection of Present Methods

Hospital beds: As has already been indicated, institutional segregation has been one of the most potent factors in the present measure of control and the recognition of its importance is indicated by the greatly increased number of available beds. However, in few sections of the country has this increase been adequate to meet the need. New York City is one example which, however, could be repeated for most of the larger towns and cities of the country.

It is generally agreed that adequate hospital accommodations for tuberculosis require at least two beds for each annual death. This, as we have pointed out, is now the responsibility of governmental agencies. Some communities, such as Detroit, Minneapolis and upstate New York, have considerably exceeded this quota. In New York City, in 1940, there were 4,055 deaths from tuberculosis and only 5,726 beds.

The need is for at least 8,000 beds. The authorities are quite aware of this situation and definite progress has been made. In the past five years, 1,391 additional beds for tuberculosis have been provided and the number of annual deaths has come down from 5,500 to 4,055, so that the situation is improved. Also 2,300 new beds are at present projected. These would take care of the

deficit but that would be several years ahead. In the meantime, the present tuberculosis hospitals are woefully overcrowded and many cases needing hospitalization are of necessity kept in their homes.

In addition to the actually sick, there are hundreds of other patients in the earliest stages of the disease which have been uncovered by the excellent X-ray surveys conducted by the Health Department, for whose care there are at present no institutional facilities whatever available. Thus many of those, who with proper care could very speedily recover, are allowed to develop into active cases, which in a few years will need far longer hospital care and will face a far more uncertain prospect of recovery.

We are all quite aware of the financial difficulties with which public authorities are confronted, but it would appear that, with the present enormous expenditures of public funds for social betterment, it is simply a question of the relative importance to be attached to the various needs. Organizations especially interested in furthering the tuberculosis hospital program, such as the Academy of Medicine and the New York Tuberculosis and Health Association, have sometimes been considered to be pressure groups for special interests. If they are such, it would appear, upon the basis of the facts, that such pressure is being applied in a quite proper direction. With our representative form of government, only a popular demand by an informed public is needed in order to make sure that the projected plans are carried out promptly.

The Negro problem: It has long been known that tuberculosis is especially prevalent in certain areas and among certain definite groups of the population.

Great progress has been made in cleaning up certain plague spots, known as "Lung Blocks," by slum clearance, by the opening of new parks in congested areas and by the construction of model, sanitary tenements.

Little, however, has been done to solve the great problem of tuberculosis among Negroes. This is largely a city problem and it is particularly pressing in New York City.

The last twenty years have witnessed a tremendous migration of Negroes from the farm and plantation to the city.

In 1920 the Negro population of New York City was 327,706. In 1940 it was approximately 450,000. In addition to them, there have also come to New York large numbers of Puerto Ricans and they behave toward tuberculosis just as do the Negroes. In 1940 there were approximately 6,500 Puerto Ricans in this city.

We have already seen that the Negro death rate from tuberculosis has been consistently three to six times higher than that of the whites and that there has been no improvement in this situation during the period that the white death rate has been progressively diminishing.

The Negro has always been much more susceptible to tuberculosis than the white, even when living under fairly favorable conditions. There can be no doubt that their removal to a crowded, insanitary city environment has greatly enhanced this predisposition.

The first important steps to remedy this situation would be a special effort to discover all existing cases by an intensive survey and to provide hospital provision for their care and segregation.

The second move would be a special effort to improve their housing and social conditions, combined with a considerable increase in the sanitary supervision and health education facilities afforded them. The same program would apply to the Puerto Ricans.

If the tuberculosis death rate among these two groups was brought down to the level of that of the whites, the death rate from this disease for the city, as a whole, would be nearer 44 than the present 54 per 100,000.

Social problems: Great has been our progress in improving general social conditions and in the relief of poverty. Much still remains to be done in nutrition, in housing, in the conditions of work and its compensation and the facilities for out-of-door recreation, such as parks and playgrounds. The general welfare is, of course, concerned here, but the indirect effect upon tuberculosis is very great.

Industrial problems: Only a beginning has been made in the control of tuberculosis in industry. While it is not specifically included among the officially designated industrial diseases, it is well known that frequently there exists a definite connection between the character and conditions of work and the incidence of tuberculosis.

In the dusty trades real progress has been made toward the protection of the worker, especially in those in which silicosis is an especial hazard, but numerous cases of silicosis still develop and very often terminate in pulmonary tuberculosis of a severe form.

Too frequently workers undertake tasks for which they are physically unsuited and tuberculosis often results. A notable instance of this is that of young women in industry. One of the lessons of the last war was this increased incidence of tuberculosis in young women who undertook unaccustomed and too arduous tasks. We are liable to see this experience repeated in the present war.

In addition to the protection afforded by the proper adjustment of hours, strains and environmental hazards, there is need of a much more wide-spread application of the system of preëmployment and periodical health examinations, which should invariably include X-ray chest examinations.

The opposition of the labor unions to this practice appears short-sighted and is probably due more to the possible misinterpretation or misuse of the findings than to the procedure itself. Properly conducted, such examinations should be much more in the interest of the workers than of the employers. The fact is that in many cases we do not know just how to act on the basis of the findings and consequently injustices may possibly occur quite frequently.

Workmen's compensation: Closely bound up with the general industrial problem is that of workmen's compensation insurance. Claims for insurance compensation in tuberculosis under present laws may be based either upon direct exposure to infection or to aggravation of a preëxisting latent disease by accident or untoward conditions during work. In the great majority of cases claims are made upon the basis of aggravation.

Although progress has been made in establishing a basis for causal relationship between the development of tuberculosis and working conditions or accidents, there still exists much confusion in this field to which varying medical opinion or testimony has added not a little. In general, it may be assumed that the more direct and prompt the claimed relationship is proven to be, the more likely is it to be causal in character. There are, however, many borderline cases and also some that are purposely rigged, which present many difficulties in the administration of justice.

The time, of course, may come when it may be claimed that in all cases of tuberculosis some compensation for wage loss and provision for care should be a community responsibility, but in the meantime it is inequitable to charge industry with it unless direct causal relationship is established beyond reasonable doubt. The natural sympathy for the worker patient operates often in his favor as against the insurance carrier for the employer, and in doubtful cases this is probably the fairer course, but there is great need for clarification of the whole situation, the responsibility for which lies largely with the medical profession.

Another important angle to this problem is the discrimination against the employment of workers who are known or are found to have had previous tuberculosis. The risk of a subsequent relapse is always present in such cases and, under the present administration of the compensation laws, there is real risk assumed by employers that such relapse may be interpreted as an aggravation with causal relationship to occupation.

With the increasing adoption of preëmployment X-ray examination, the number of such cases is increasing rapidly and in the case of those who have had definite clinical tuberculosis which has been arrested, the obstacle to reëmployment is still greater. Carried to an ultimate logical conclusion, the object of successful treatment, which is a return to normal, self-sustaining life, would be defeated. This situation is further complicated by the fact that such workers with arrested tuberculosis cannot legally in most states waive their rights under the compensation act.

This complicated problem awaits satisfactory solution and demands careful study by legislators, lawyers and all others interested in social justice, as well as by physicians.

Rehabilitation: In the treatment of tuberculosis it is well recognized that, after the rest or collapse treatment of the active phase of the disease, there must ensue a long difficult period in which gradually increased activities are allowed under supervision before a return to normal life is permissible. One of the most frequent causes of relapse is the failure to continue this period long enough or under proper supervision.

Part of this task is the function of the sanatorium but, following discharge from the institution, a period of after-care is essential if the patient is to be permanently rehabilitated. In general, at present the ultimate success attained depends upon the intelligence and education of each individual patient, the care with which he is periodically examined and the wisdom of his medical adviser.

Attempts have been made upon a small scale to supply this after-care to groups

of patients in rehabilitation centres. These have been mainly small private enterprises, but lately a beginning is being made to organize such centres under government auspices, supported by social security funds. As yet these efforts are small and inadequate but the need for meeting this problem of after-care is being more generally recognized, but the realization of any systematized and really effective movement in this direction appears to be very far distant.

The significance and treatment of preclinical lesions: We have already emphasized the importance of the minimal X-ray lesions discovered in the course of routine general examination, by X-ray surveys of groups of the supposedly well and by preëmployment examinations. In the main, these cases present no abnormal symptoms or physical signs, yet it is believed that from them will develop many of the cases of disabling tuberculosis of the future. We have already indicated that in each individual case the significance of these findings is by no means certain and the proper methods for their treatment still less so.

We know that many of these lesions remain entirely latent and innocuous throughout life, but we also know that from many others active disease develops sooner or later. The great importance of distinguishing between these two categories is obvious; in other words, to recognize which of them are potentially dangerous and which are not. The present resources of our clinical knowledge do not give us any satisfactory answer to this question. Consequently the same uncertainty exists as to how these patients should be advised and treated.

Roughly speaking, these cases are being handled in one of four ways.

First, they are advised that the X-ray findings are fortuitous, unimportant and innocuous and consequently may be ignored and entirely normal life continued.

Second, they are advised that the findings may or may not be significant, that the patient should continue a fairly normal life but avoid strains and excesses, be on the lookout for suspicious symptoms and be checked up by periodic X-ray films at intervals variously fixed at three, six or even twelve months.

Third, they are warned more seriously of the possibilities and advised to stop work, take a modified rest-cure with a good deal of open-air life under regular medical supervision with X-ray films once a month, preferably in a sanatorium. This does not involve the strict rest-cure enforced for active cases and if all goes well in three or four months the return to active life with the limitations and the periodic examinations recommended in the second category.

Last, there are competent and conscientious physicians who advise that all such patients be treated as active cases with strict bed-rest for several months, followed by graduated exercise under supervision for the remainder of a year. Such a program would entail the need for many additional beds not now available or projected, for these cases are being uncovered by the thousands.

It is thus obvious that these modern methods in the diagnosis of minimal cases of tuberculosis, or at least of tuberculous lesions, have opened up an important field for future study and investigation.

What appears to be needed is a careful clinical study of large groups of these

cases under carefully controlled conditions in the hope that in this way fairly accurate criteria might be established by which to judge the significance and the indications for treatment in each individual case.

Problems Involving the Acquisition of New Knowledge

It is clear that there is no sharp line of demarcation between those problems which we have designated as requiring the perfection of present methods for their solution and those which involve the acquisition of knowledge in definitely new fields. Some of the questions already discussed entail the acquisition of new knowledge in part, but those which we are now to consider more definitely require scientific investigations, both experimental and clinical for their solution.

Nutrition: A new science of nutrition has developed since the discovery of the important rôle played by vitamins. Although in tuberculosis it has long been appreciated that faulty nutrition is a factor in its development, this idea has been based almost exclusively upon the caloric value of food. Up to the present time, although in the light of our new knowledge the possibility that vitamin content may be at least equally important, there is as yet no exact knowledge upon which to base this hypothesis.

To be sure, for a century, upon entirely empirical grounds, codliver oil has been considered of value and also vitamins A and B, as well as D, have been conjectured as probably important; still their rôle is uncertain and our knowledge of their possible importance imperfect. By analogy with other chronic diseases, it would seem very improbable that vitamin deficiency is not an important factor in tuberculosis which thus may be, especially in its more chronic and insidious forms, considered as a deficiency as well as an infectious disease.

Rapid progress is being made in this whole field of research and the study of vitamins in relation to tuberculosis is already in the program. Results from such studies will be eagerly awaited and may well materially influence our ideas of the prevention and also the treatment of this disease.

Age and sex: It has long been recognized that children below the age of two are very susceptible to tuberculosis and that the mortality from it among this age group is very high. Also it is realized that from the ages from two to twelve years the mortality is surprisingly low. The differences in sex do not appear to affect the situation in either of these two age groups.

It has also been definitely shown by experience and statistics that in the adult and middle-age groups the incidence and mortality from tuberculosis is regularly higher among men than among women. The hazards and strains of life appear to be largely responsible for this difference.

Too little attention has been focussed upon the intermediate age period of puberty and adolescence. Here the greatest importance appears to lie in the question of sex. Physiological changes at puberty are greater in females and this would suggest some possible relationship between these changes and the fact that girls of that age are more susceptible than boys, but in both sexes it is to be noted that the comparative immunity already noted among children be-

tween the ages of two and twelve definitely changes over to an increased susceptibility which makes a latent tuberculous infection definitely more dangerous during the puberty period.

Another fact of significance is the increased susceptibility of adolescent girls in their teens when they encounter social and economic stresses at that age. This was strikingly shown in England during and after the last war, when the incidence of and mortality from tuberculosis increased remarkedly among these young girls and women. This has probably been accurately ascribed to the large number of these girls who were taken into industrial life in order to replace the men. This is an important fact to be borne in mind in connection with the present world war, as will be discussed again later.

My present object is merely to call attention to these age and sex factors which are constituting a problem too little understoood and about which comparatively little is being done. It is another one, therefore, concerning which we need new knowledge and new efforts.

Constitution: It has long been known that there are wide differences between individuals, families and races in their susceptibility to tuberculosis.

Various clinical observations have shown that, under exactly similar conditions of exposure to infections, some of a family will develop definite tuberculosis and others may not even show a positive tuberculin reaction. Also, with identical latent or early lesions, some go on to progressive disease and others never become ill.

Even more striking is the difference between races. The Jews are resistant and, when disease develops among them, it is apt to be in a mild form. Upon the other hand, the Negroes and the Indians and the Irish are unusually susceptible and with them the disease is apt to be severe, even malignant.

Various explanations have been offered. The virgin soil theory states that in uninfected individuals the disease behaves in the same acute manner as it is apt to do in the case of previously uninfected infants. Untoward social conditions and bad personal habits have been thought to partly explain the phenomenon. Racial immunity acquired by the infection of succeeding generations which has been successfully resisted is another theory. This assumes the inheritance of an acquired characteristic, which biologists have long held to be impossible, but are now reconsidering.

None of these possible explanations appear quite adequate. In recent years there has been a revival of scientific interest in the problems of the body constitution as a whole in its relation not only to tuberculosis, but also to other diseases.

Many interesting studies have been undertaken in this field. Quite recently, Lurie at the Phipps Institute has published some very suggestive results of animal experiments along this line. Apparently he has been able to show that definite variations in the capacity of the body tissues to resist tuberculous infection occur in animals bred according to certain controlled hereditary influences.

Although as yet no definite knowledge applicable to human disease has been

presented, nevertheless many observers believe that we will hear much more of constitutional factors in tuberculosis, as well as other diseases, in the near future.

In this connection it is interesting to recall the fact that before Villemin, and later Koch, determined the infectious nature of the disease, the generally accepted notion of the underlying cause of tuberculosis was a diathesis, that is, a constitutional condition. Would it not be illuminating should we discover that those clinicians of a century ago, mingled with their ignorance, had some truth on their side based only upon empirical or clinical observations?

Specific therapy: Up to the present time our only successful methods in the treatment of tuberculosis have been by indirect methods of approach, dependent largely upon conserving and strengthening the resistance of the body to the infection. All through the sixty years since Koch's discovery the dream and the aim of all serious workers in this field have been the development of some method of direct specific attack upon the tubercle bacillus. As already outlined, the chief efforts in this direction, beginning with Koch himself with his hopes in tuberculin, have been along biological lines connected with attempts to produce bacteriological immunity. Some results suggesting partial success in animals have served to keep alive this fascinating quest, but they have all failed to realize our hopes.

Chemotherapy was tried with especial emphasis upon the use of the heavy metals, such as copper and gold, but it was not until the dramatic success of the sulfonamide group of chemicals with other infections that the possibility of the achievement of successful chemotherapy in tuberculosis was seriously entertained. Active experimentation with these drugs is now under way, with some hopeful results in animals as already cited, and it would appear that at present the hope for a specific remedy is now brighter in the field of chemotherapy than in any other direction.

Nevertheless, it is still the fact that we know of no specific cure for tuberculosis and that, until such is found, all of our present methods are only partially and inadequately successful. If and when we have such a specific, then it may well be that all of our present laboriously built structure, both for treatment and prevention, will be discarded as no longer needed.

The real goal, therefore, of all efforts is to find this specific cure and the restless inquiring minds of true investigators will be satisfied with nothing less. This is the greatest challenge of the future in our fight against tuberculosis.

The effects of the war: With this background of the progress of our knowledge of tuberculosis which we have cursorily reviewed, it appears timely to conclude with a few observations upon the possible effects of the present world war. In the face of such a cataclysm, many of the treasured achievements of our civilization are seriously endangered and among them the health of the peoples of the world. The greatest immediate danger is in other lands, particularly in Europe, but the United States may very well become involved to a considerable, if not to a serious degree.

Disease and pestilence have always followed conditions similar to those which

now exist and tuberculosis is one of those to be dreaded. The groundwork for this insidious infection has always been conditions of poverty, physical and mental stress, inanition or starvation, the breakdown of sanitary control and the increased opportunities for contact infection. After the last war, in Central Europe and in conquered territories, the death rate from tuberculosis tripled within two or three years. Present conditions there are infinitely worse with wide-spread destitution, suffering and starvation, and it may be expected that the results will be correspondingly bad.

We have already commented upon the results in England among girls and young women inducted into unaccustomed industrial occupations. A similar situation may well arise here in the near future.

We live in a land of plenty but we already face the introduction of rationing cards, especially in sugar, and the dislocation of large groups of the population from their accustomed conditions and habits of life may well result in unforeseen inequalities of food distribution. Fortunately the newer science of nutrition is available and will help, but it is not yet complete, nor is it generally accepted and applied.

We are also facing longer hours and greater pressure for labor and serious housing difficulties in the rapidly extending new industrial communities. As the war goes on, we are to feel more and more the strain of it with accompanying diminished physical resistance.

In the armed forces we are starting with a great advantage over 1917, as far as tuberculosis is concerned. Although in that war, where participation was relatively short, yet as a result of it, either directly or indirectly, about 140,000 individuals became dependent upon the government because of tuberculosis, with an eventual aggregate cost to date of $959,000,000. This tremendous cost was partly due to the generous policy adopted by the government, but the number of cases of tuberculosis was in large part due to the fact that men were taken into the Army and Navy without the careful examination by X-ray, which would have eliminated those who, at the time of enlistment, had already evidence of tuberculosis in their lungs in some form.

This time, the routine chest X-ray films which have been taken of all enlisted and selected men have eliminated many who would otherwise have been accepted; consequently a very marked dimunition in the incidence of tuberculosis in the Army and Navy can be confidently expected. The main danger during this war, therefore, will be to the civilian population.

There is added danger due to the possibility of the interference with public health services which can only be met by a realization of their great importance in defense in safeguarding the health of the people even more zealously than in normal times.

Not only must our health practice be continued but, with the laboratories of all the rest of the world disrupted, the United States alone remains to keep alive research into possible methods of preserving life rather than concentrate entirely upon those of destruction. Under the emotional stress of the natural eagerness to participate directly in the war effort, it would be easy to conceive that these

fundamentally important activities might be, at least temporarily, neglected, which would be indeed a serious loss to this as well as to succeeding generations. In general it should be realized that conditions accompanying or following the war may well contribute to increase of disease and perhaps of tuberculosis.

It would appear justified, therefore, to state in conclusion as we did at the outset, that any idea that tuberculosis is conquered is premature. A disease which we know to be preventable and yet caused the death of 61,000 persons in the United States and of 4,000 in New York City in 1940, cannot be said to be conquered; it is only relatively controlled.

The tuberculosis campaign is not yet a conquest; it still constitutes a major challenge.

SUMMARY

The chief factors in the success of the antituberculosis campaign from 1900 to 1940 are very briefly noted as they are strikingly shown by the diminution of the mortality for tuberculosis in New York City from 300 to 54 per 100,000 of population and in the United States from 200 to 46, between 1900 and 1940.

The main part of the essay is devoted to a discussion of problems still confronting us before tuberculosis can be considered conquered.

These problems are considered in two main categories:

1: Those involving perfection of present methods.
2: Those involving the acquisition of new knowledge.

In the first category is emphasized (*a*) the extension of the number of institutional beds for segregation and for modern treatment, (*b*) the at present unsolved problem of the control of tuberculosis among Negroes, (*c*) the need of intensification of efforts to control the disease in industry with emphasis upon both sanitary conditions and periodic health examinations, especially by chest X-rays, and closely associated with them the problems of workmen's compensation and of the industrial rehabilitation of arrested cases, (*d*) the preclinical detection of minimal lesions, especially by means of X-ray surveys and their subsequent management. This important problem is discussed in some detail and the inadequacy of the present situation is presented. It is mainly from those cases that the disabling tuberculosis of the future will come.

In the second category, (*a*) the importance of the newer science of nutrition is discussed in relation to tuberculosis, (*b*) the implications of race and sex are reviewed, (*c*) the possible rôle of body constitution in the susceptibility to the disease is raised, (*d*) the ultimate goal of a specific cure for tuberculosis is emphasized and the history and present trends in its search are indicated, (*e*) the possible effects of the present war by greatly increasing the amount of tuberculosis are discussed, based upon past experience and upon conditions which may beexpected to result during and after the war.

In conclusion it is pointed out that a preventable disease which killed 4,000 persons in New York City and 61,000 in the United States in 1940 cannot be considered conquered.

The antituberculosis campaign, therefore, is not as yet a conquest, but rather still presents a major challenge.

SUMARIO

Preséntanse aquí sucintamente los principales factores que han intervenido en el éxito de la lucha antituberculosa librada de 1900 a 1940, según se manifiesta en forma notable en la disminución de la mortalidad tuberculosa en la ciudad de Nueva York de 300 a 54 por 100,000 habitantes, y en los Estados Unidos de 200 a 46.

La principal parte de este ensayo está dedicada a la discusión de los problemas que todavía nos confrontan, antes de poder considerar como conquistada la tuberculosis.

Estos problemas corresponden a dos categorías principales:

1. Los que exigen perfeccionamiento de los métodos actuales.
2. Los que exigen adquisición de nuevos conocimientos.

En la primera categoría recálcanse: (*a*) aumento del número de camas en las instituciones dedicadas a la segregación y al tratamiento moderno; (*b*) el problema todavía irresuelto del dominio de la tuberculosis en los negros; (*c*) la necesidad de intensificar los esfuerzos dedicados a combatir la enfermedad en la industria, recalcando tanto los factores higiénicos como los exámenes físicos periódicos, en particular por medio de roentgenografías torácicas, e íntimamente asociados con ellos los problemas de la indemnización obrera y de la rehabilitación industrial de los casos estacionados; (*d*) el descubrimiento preclínico de las lesiones mínimas, en particular por medio de censos radiográficos, y la atención subsecuente de aquéllas, dedicándose bastante espacio a este problema importante, y señalándose lo inadecuado de los métodos actuales, pues es principalmente de estos casos que provendrá la tuberculosis incapacitante del futuro.

En la segunda categoría menciónanse: (*a*) la importancia de la nueva ciencia de la nutrición en relación con la tuberculosis; (*b*) los datos relativos a la raza y sexo; (*c*) el posible papel de la constitución orgánica en la susceptibilidad a la enfermedad; (*d*) recálcase la meta definitiva de una curación específica para la tuberculosis, y se apuntan las tendencias actuales en su investigación; (*e*) los posibles efectos de la guerra actual, que acrecentarán considerablemente la difusión de la tuberculosis, en lo que cabe juzgar por la experiencia del pasado, y las condiciones que pueden esperarse durante y después de la guerra.

Al concluir, señálase que no cabe considerar dominada una enfermedad prevenible que mató a 4,000 personas en la ciudad de Nueva York y 61,000 en los Estados Unidos en 1940, por lo cual en vez de adjudicarse la victoria a la lucha antituberculosa, debe considerarse todavía como amenaza que desafía nuestros esfuerzos.

IMMUNITY IN TUBERCULOSIS

Clinical Considerations

F. M. POTTENGER[1]

THE NATURE OF IMMUNITY

Of the many valuable contributions to our knowledge of tuberculosis which were made by Allen Krause, those relating to immunity are of outstanding interest. So it is fitting to discuss the subject in this Memorial Issue.

It may be said truly that the tuberculous patient cures himself or kills himself by his own infection, meaning that each reinoculation which is within his capacity to defend himself increases his total resistance, and each reinoculation which is too large for him to counteract lowers his total resistance. Cure depends upon developing an increase in resistance or immunity to bacilli and bacillary substances. What will happen depends upon the character of the infection, that is, the number and virulence of the bacilli and the state of the host at the time. There is no chance of healing taking place if immunity fails, for immunity alone is able to protect against the multiplication of bacilli and their spread in the tissues and to bring about healing of the lesion. This may be understood by comparing primary infection produced by a sufficiently large number of bacilli to cause a disease which spreads rapidly and produces early death, with a chronic advanced disease in which the numbers of bacilli in the tissues are equally large and the opportunity for metastases forming is continuously great, and yet the disease advances slowly, if at all; in fact, may heal.

It is necessary that we attempt to understand of what this increased protection consists, how it is developed and how it performs its service. The fact that our opinions are confused calls for careful discussion rather than discouragement.

Koch made the first observation of the immunity mechanism at work in tuberculosis when he noted the difference between the local reaction caused by an inoculation of bacilli into a healthy and into an infected guinea pig. In the healthy pig he noted that the inoculation was followed at first by little more than the trauma caused by the injection, but that this enlarged to a fair-sized nodule in one, two or three weeks, according to the number of bacilli in the inoculum, after which it went on as a progressive process. In the tuberculous pig he also noted that an inflammatory reaction appeared at the site of infection, but this came on quickly in a few hours after inoculation and increased in severity; and, like that in the healthy pig, became nodular in about two weeks' time, but thereafter the course differed—it became retrogressive.

The important thing to stress in these observations is that in the nontuberculous pig the reaction is slow in appearing but the disease progresses, while in the tuberculous pig the reaction develops quickly but comes to a standstill and then

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proceeds to retrogress. This shows that a change is brought about by the first inoculation which increases resistance. The mechanism responsible for this difference is recognized as immunity. It is a mechanism of many phases, affecting many tissues and involving many functions.

While immunity in tuberculosis is only relative, it is far from being a negligible mechanism. Clinicians, as a rule, give insufficient attention to it, for it is the most important factor in determining the character and course of the disease and a necessary one in healing. Experiments such as those of Koch, von Behring, Römer, Hamburger, Bartel, Wolff-Eisner, Löwenstein, Wright, Raw, Trudeau, Gilliland, Webb, von Ruck, Krause, Willis, Rich, Opie, Sewall, Menkin, Sabin, Lurie and many others, should be carefully studied by every one who treats tuberculosis, for they elucidate the basic facts of defense and healing. While many of these experiments can be criticized as having been carried out with inoculations of bacilli in which the numbers were far too large, thus failing to approach conditions of natural infection, yet they indicate how the host reacts to his disease.

Attempts have been made to separate the various phases of immunity; but this, from my understanding of the subject, is not only impossible but regrettable. It causes much confusion. Allergy has been associated largely with the inflammatory exudative reaction and, because of the violence of the reaction at times, there are those who see in it only harm to the host. Some speak of allergy in contradistinction to immunity. This is illogical. It perhaps would have saved confusion had the term "allergy" not been injected into our conception. We must understand it as being only one phase of tissue sensitization, while immunity includes all specific protective phenomena. In immunity we must consider that tissues, in the widest sense, body fluids, wandering cells as well as fixed cells, are sensitized to the invading microörganisms so that their action may be rendered more effective in protecting the host. If we define immunity in infection as an altered reaction of the host necessary to protect it from invading bacteria, we cannot help seeing that it is not only an inflammatory, exudative phenomenon caused by allergen-antibody reaction, but that it includes other altered reactions which exert an antibacillary effect and an inhibiting effect upon the multiplication of bacilli, and a favorable effect upon the production of tubercles; in fact, it is the whole defense picture.

It seems to me to clarify our ideas if we look upon the preponderantly exudative process, which is usually termed allergic, as a less complete, early phase of immunity; and look upon total specific defense as a later and more effective immunity. If one will analyze all known factors in immunity, he will see that they are all evidence of quickened and enhanced physiological functions brought about to meet the particular phase of infection present at the time. The thing that reinoculation does to the reaction is to hasten it and increase its efficiency. Immunity is always a protective and healing process, without which probably no tuberculous infection could heal, but a process the efficiency of which must be built up *pari passu* with the infection against which it protects.

HOW IS IMMUNITY PRODUCED?

If we attempt to understand the difference in reaction of the normal and the tuberculous animal to bacilli and bacillary products, we shall find the answer in the entire category of intimate phenomena called out to resist infection.

When bacilli enter the the tissues they attempt to destroy the local cells and convert them into pabulum to serve their needs during multiplication and growth. The cells of the body, on the other hand, attempt to destroy the bacilli and to check their development and growth. First infection meets less opposition than reinfection. As a result of this tissue-bacillus struggle, bacilli are destroyed and bacillary fractions in increasing amounts are set free into the tissues which they sensitize to further contact with bacillary products. Thereafter, when contacted by bacilli or bacillary proteins, the cells respond quickly with inflammation and exudation. If the same protein which sensitizes continues, in amounts which are not too large, to act upon the cells, it may cause desensitization and other phenomena such as a slower multiplication and an increased destruction of bacilli, and a more rapid and extensive tubercle formation, which indicate that the resistance of the host has been substantially increased. These are all phases of the increased resistance which we call immunity.

Man's normal physiological response may be sufficient to protect him against slight stimuli of various kinds; but, when stimuli are greater, an abnormal response is required to make the protective mechanism effective. This is true no matter what the nature of the stimulus.

The relation of physiological response to the type of force making the attack is shown in comparing protection against such diversified dangers as an approaching enemy and an infection. The reaction which prepares for defense or flight in case of the former is primarily an emotional response which is expressed through both the voluntary and involuntary nervous systems, through the glands of internal secretion and the electrolytic system. It is primarily an exaggeration of normal emotional reactions and accordingly initiates abnormal physiological response.

The reaction against bacteria in disease-producing numbers likewise consists of an increase in intensity of physiological response. It consists of increased cellular, nervous, hormonal and electrolytic reactions. It is an intensification of those functions of the body by which it normally is able to digest, destroy or retard growth and movement of bacteria and various fractions of bacteria should they gain entrance to the tissues in small amounts.

The important point is that ordinary defense is a normal physiological process, and immunity a heightening of these same physiological forces. They depart from normal activity because they are required to do so in order to be able to meet new and unusual stimuli.

The body, under normal conditions, is able to digest a limited amount of protein—either of bacterial or nonbacterial origin—which may gain access to the tissues. Each cell that enters into the structure of complex organisms car-

ries with it, as it evolves from lower life, a digestive function similar to that possessed by the simple unicellular amoeba. This comes into use in protecting it against bacteria or injurious foreign protein which gains access to the tissues. In case of infection probably the chief manner in which tissue digestion differs from normal cellular digestion is in the ever increasing amount of protein which it is obliged to destroy. Immunity against infectious disease, then, may be said to consist of the processes which the host marshals to digest, destroy or protect itself against bacteria and bacterial products which gain access to the tissues in amounts which, if not destroyed, would injure or threaten the life of the individual.

Immunity in tuberculosis starts to develop as soon as the infecting bacilli begin to multiply and the bacillary products in minute quantities begin to make their escape into the tissues. Our conception here includes not only solid tissues but the fluids of the body as well.

EFFECT OF IMMUNITY IN TUBERCULOSIS

What is the effect of the altered physiological reaction which we call immunity in tuberculous disease?

By comparing the phenomena which attend primary experimental infection with those of reinfection, certain facts may be noted which show that the two conditions differ in important features. In primary infection there seems to be a very inadequate protection and bacilli quickly pass to the regional lymph nodes; and, furthermore, if the number of microörganisms is large, they readily pass beyond these barriers and make a circuit of the body, infecting the viscera. On the other hand, in infection produced by reinoculating a tuberculous animal with similar numbers of bacilli a greater degree of protection is shown for the microörganisms are fixed and detained at the point of inoculation. They do not find ready passage through the tissues. Only slowly and in comparatively small numbers do they gain access to the regional lymph nodes, and still more slowly do they make the circuit of the body and infect the viscera. This was shown by Krause. He infected animals with a bacillus of known low virulence and later reinoculated certain groups of them, as well as groups of normal animals, with a strain of greater virulence. The two strains were so different that the latter could be readily differentiated from those which caused the primary infection. The more virulent bacilli spread rapidly and in great numbers to the viscera of the normal animals, but the viscera of the infected animals were involved tardily and showed evidence only of mild infection, thus proving that the primary infection had produced a marked protection.

In a tuberculous host, whenever bacilli or bacillary protein (tuberculin) comes in contact with the sensitized fixed cells, reaction occurs. This reaction is an antigen-antibody reaction taking place with the antibody while attached to the cell. It is evidence of protection. At first the reaction consists of inflammation with exudation and an outpouring of wandering cells; but it is also accompanied by proliferation. However, as immunity increases, the cells become less sensitive and the inflammatory exudative elements of the reaction

become less prominent, while the bacilli are inhibited in their multiplication and growth and proliferation becomes more evident.

The allergic, inflammatory, exudative reaction takes place when the cells are highly sensitized. In clinical practice it is particularly the lesion of adolescence and young adult life. It appears when reinfection is caused by comparatively large numbers of bacilli, before the host has developed relative desensitization and the marked ability to inhibit growth and multiplication of bacilli and the increased power to destroy bacilli, which it develops after it has had many reinoculations of small numbers of bacilli. In this relatively early type of lesion the chief factor in defense is the seizing and anchoring of bacilli by inflammation and tubercle formation and interfering with their spreading in the tissues. Thus the host is protected from what, without it, might be an extensive invasion.

While the inflammatory reaction may detain relatively small numbers of bacilli in the foci of infection, there is nothing that will explain the survival of a patient with active wide-spread tuberculosis, except a highly developed power of the body tissues to protect the individual from a constantly increasing number of bacilli. If the patient is to survive, multiplication and spread of bacilli must be inhibited and an increased ability to destroy them, as well as an increased ability to wall them in by tubercle formation, must be developed. Without this greater protection no individual could survive after bacilli once gain access to his tissues in large numbers; for, unhindered, they would multiply and spread in great numbers.

If many bacilli gain access to the lower air passages of normal individuals, infection will readily take place. We have observed this in animal experimentation and in the early primary infections that we meet in children. When a patient has advanced ulcerative tuberculosis, on the other hand, millions of bacilli may pass over the mucous membranes of the same air passages daily and be forced into the finer air passages by cough without further infection taking place and with the disease healing. Furthermore, in advanced tuberculosis we must assume that, frequently, great numbers of bacilli gain access to the blood stream without infection following; so they must be restrained from forming new foci by some effective mechanism which is not competent in the noninfected. This increased protection also explains the fact that visceral infection is not common in tuberculous patients except as the end of life approaches and the immunity is rapidly vanishing.

Further clinical proof of increased resistance or immunity is furnished by the fact that, while chronic tuberculosis is a series of episodes of reinfection, some with few, others with many bacilli, if the new foci are not caused by too many bacilli they are usually relatively mild and many of them prove to be abortive. This is particularly true of the metastases which occur in patients who are treated according to modern physiological principles by which the protective body functions are kept at a high point of efficiency.

That there is a difference in the mechanism required to protect the host in early and late tuberculosis is self-evident; for, if the body cells remained as

highly sensitized to bacilli and bacillary substances throughout the course of advanced tuberculosis as they are in the period of early infection, the reaction to the many bacilli which form metastases would destroy the patient. In fact, there would be no chronic tuberculosis. It would be an acute, rapidly destructive disease.

Still further evidence of the protective influence of a tuberculous infection is provided in case a patient has tuberculosis of some particular organ, for example, the lung, kidney or bone. If later another organ becomes infected, the disease is apt to be mild in character. An exception to this is found, as mentioned above, in the late stages of severe pulmonary tuberculosis when immunity is markedly depressed and the host is losing his power of resistance. Under these circumstances it is not uncommon to have the larynx and intestines involved.

Healing results when the immunity mechanism becomes so competent that bacilli no longer multiply and spread, when the products of exudation and necrosis have been removed from the diseased area and when all remaining bacilli and bacillary products have been killed or walled in by living cells. The patient dies of his tuberculosis when his immunity mechanism has been so overtaxed that it is no longer able to respond to the specific stimuli which originate in the foci of disease.

IMMUNITY AND COMPENSATION IN HEALING

Immunity alone will not cure all cases of tuberculosis any more than the knife will cure all cases of appendicitis. However, during the time of early invasion if immunity could be raised to a high efficiency, cure would usually be brought about. But clinicians as a rule do not have the choice of treating early invasion. They are devoting their time and directing their skill largely toward overcoming the ravages of advanced and advancing disease, which injects many problems which do not belong to the early stage of the disease.

We are apt to have a wrong conception of what constitutes curable tuberculosis. Extent of lesion and cavity are given too much attention in forming a prognosis. There are certain types of cavity which make their appearance early and heal readily and certain extensive lesions which are favorable for cure, if only we will aid the patient physiologically to react efficiently.

Compensation is also an important factor in healing. It is only second to immunity in importance. The more extensive and the more destructive the process, either in tissue elasticity or tissue volume, the greater the compensation which must take place. Compensation in early invasion is simple and consists largely of reduced movement, mild emphysema of the tissues adjoining the infiltration and an almost insignificant contraction of the bony cage. In advanced, destructive lesions, on the other hand, marked emphysematous changes may take place, enlarging the lung volume; intercostal spaces may narrow, making the thoracic cage smaller; the contralateral lung may enlarge and the mediastinum may shift from its central position toward the affected side; the diaphragm may become elevated—all for the purpose of maintaining an equi-

librium between the lung volume and the size of the bony thorax. In certain instances, regardless of these attempts at adjustment, compensation may be insufficient to overcome the tension on the tissues and to permit the walls of cavities, large and small, to approximate so that the patient's healing power may act efficiently. In many instances in which natural compensation is insufficient, aid may be brought to the patient artificially in the form of therapeutic pneumothorax, operations on the phrenic nerve, severing adhesions and thoracoplasty. These are now universally recognized as valuable and necessary aids in such instances.

Healing of tuberculosis, as we meet it in clinical practice, is, when accurately analyzed, a combination of immunity and compensation. Immunity depending upon physiological processes is enhanced by all measures which will improve the general condition of the patient. Compensation is a mechanical process and may be aided either by such measures as will relax or compress the diseased lung tissue or diminish the capacity of the bony cage. In practice, it is too often forgotten that, no matter what mechanical assistance is given, measures which improve physiological stability and enhance those particular physiological processes which are utilized in creating immunity are necessary in order to bring about healing. The reverse is equally true. No matter how high the immunity, tissues that cannot relax or contract, especially if cavitation is present, heal with difficulty or do not heal at all.

TUBERCULIN AND IMMUNITY

If a tuberculous infection produces changes in the reaction of the tissues of the body so that it heals itself by bringing about immunity, and if the principal fractions of the bacillus which are active in creating immunity and in increasing it when created are bacillary proteins, then it seems reasonable that these proteins should have value when administered therapeutically.

It is particularly significant that an animal's resistance can be increased by the use of dead bacilli. While there may be other fractions than the proteins which are necessary in order to bring about the fullest measure of immunity, studies so far do not indicate what they are. Whole bacilli, dead or alive, will produce sensitization, and their reinoculation in doses which are not too large will produce desensitization and a more complete immunity. This is in line with the experience of desensitizing cells in the so-called allergic diseases by using the specific allergen. Desensitization is an important factor in defense in chronic tuberculosis. It is associated with resistance and healing.

Contrary to usual opinion, tuberculin may be used advantageously in acute exudative tuberculosis. I have noted in many extensive exudative lesions what seems to be a more rapid desensitization of the tissues, a more rapid absorption of the exudate and a more rapid fibrosis than occurs without its use. It has generally been recognized that tuberculin is of value in the treatment of chronic advanced lesions which are more or less quiescent but fail to heal. Its value seems to be in its ability to increase fibrosis and to clear the field of the products of exudation.

With a knowledge of tuberculosis and a knowledge of the immunity reactions one is able to administer tuberculin with a confidence of being able to control reactions so as not to cause stimulation beyond that which is desired.

There is often great fear that tuberculin will reactivate quiescent lesions. This is usually expressed by those who have had little or no experience in its use. I have seen none of the disasters that so many fear; on the contrary, I have seen great benefit result from its use. While it is not a perfect immunizing product it comes nearest to having the immunizing properties of viable bacilli of any remedy that we possess. No remedy is perfect or sufficient in the treatment of tuberculosis. None will heal the lesions quickly; but each one should be used for what it is able to contribute to cure. Tuberculin is the only remedy that we have which imitates the stimulation which bacilli, themselves, produce, and has the advantage of being under the control of the physician.

SUMMARY

1. The tuberculous patient cures himself or kills himself by his own infection. Infrequent small reinoculations bring about fibrosis and healing. Frequent large reinoculations cause destruction and spreading of the disease.

2. Allergy is discussed as being an intimate part of the total immunity reaction.

3. Man's normal physiological response may be sufficient to protect him against mild invasions, but a quickening and a heightening of physiological response is necessary to protect against more serious infection.

4. The effect of immunity in tuberculosis is to lessen the danger of reinoculation and to make the reaction of the body more favorable to healing in case infection occurs.

5. Immunity checks the spread of bacilli in the body, interferes with the multiplication of bacilli, increases the host's power to destroy bacilli, hastens tubercle formation and increases fibrosis.

6. Immunity is essential to healing but cannot produce the result unless a proper compensation can take place between the pulmonary tissues and the thoracic cage. This compensation may be brought about naturally by: (*1*) emphysema developing in the pulmonary tissues, (*2*) shifting of the mediastinum, (*3*) elevation of the diaphragm and (*4*) contraction of the bony cage. The purpose of all these compensatory measures is to restore equilibrium between the lung volume and the thoracic space.

7. In cases where compensation cannot be produced naturally, it may be aided by pneumothorax, operations on the phrenic nerve, the severing of adhesions, and thoracoplasty; but immunity must still heal the lesion.

8. The action of living bacilli in creating immunity and stimulating healing may be imitated by dead bacilli. Bacillary proteins (tuberculin) are recognized as the active factors in producing these effects. Tuberculin will not produce all of the reactions of the tubercle bacillus, but when used therapeutically will produce many of the effects which are necessary to healing. It has a logical basis for use, though it is not a perfect immunizing agent.

SUMARIO

1. El tuberculoso se cura o se mata con su propia infección. Las pequeñas y raras reinoculaciones provocan fibrosis y cicatrización, mientras que las frecuentes y grandes producen destrucción y difusión de la enfermedad.

2. Discútese la alergia como parte íntima de la reacción total de inmunidad.

3. La respuesta normofisiológica del hombre puede bastar para protegerlo contra las invasiones leves, pero para resguardar contra una infección más grave se necesita la avivación y realce de la respuesta fisiológica.

4. El efecto de la inmunidad en la tuberculosis es mermar el peligro de la reinoculación, y hacer la reacción orgánica más favorable a la curación en caso de que sobrevenga infección.

5. La inmunidad cohibe la propagación de bacilos en el organismo, impide su multiplicación, refuerza la facultad del huésped para destruirlos, acelera la tuberculogenia y acrecienta la fibrosis.

6. La inmunidad es esencial para la curación, pero no puede producir tal resultado a menos que tenga lugar la debida compensación entre los tejidos pulmonares y la caja torácica. Esta compensación puede obtenerse naturalmente por: (*1*) formación de enfisema en los tejidos pulmonares; (*2*) desviación del mediastino; (*3*) elevación del diafragma; y (*4*), contracción de la caja ósea. El fin de todas estas medidas compensatorias es restablecer el equilibrio entre el volumen pulmonar y el espacio torácico.

7. En los casos en que no puede producirse naturalmente compensación, puede ayudarse con el neumotórax, las operaciones en el nervio frénico, la resección de las adherencias y la toracoplastia, pero a la inmunidad le corresponde todavía la curación de la lesión.

8. La acción de los bacilos vivos en la creación de inmunidad y estímulo de la cicatrización puede ser imitada por los muertos. En la producción de estos efectos las proteínas bacilares (tuberculina) están reconocidas como los factores activos. La tuberculina no producirá todas las reacciones del bacilo tuberculoso, pero empleada terapéuticamente sí producirá muchos de los efectos necesarios para la curación. Hay, pues, base lágica para su empleo, aunque no constituye un perfecto elemento immunizante.

FEATURES OF THE EARLY PULMONARY INFILTRATION

J. BURNS AMBERSON, JR.[1]

The greatest obstacle to understanding the behavior of the earliest lesions of pulmonary tuberculosis is their failure to sicken the host. Access to the problem can be had only by a systematic study of groups of healthy people among whom, in time, the disease may be expected to appear. Since, next to absolute prevention of infection, identification and proper management of the early lesion is the most effective means of attack on tuberculosis, the importance of the study can easily be seen. Reports of various investigators have been published, most of which include observations of lesions by the X-ray, while they are still undetectable by other methods. At Bellevue Hospital a somewhat similar study has been under way for more than thirteen years, and the views which I am expressing here in a general way are based largely on this experience.

It has been variously stated that a person is unlikely to become a phthisic if he has passed the age of thirty or thirty-five without a demonstrable pulmonary lesion. If we except older people whose resistance has been depleted by uncontrolled diabetes, dietary deficiences, alcoholism, and the like, the statement holds. Furthermore, it is observed that the lesions of progressive pulmonary tuberculosis usually do not appear until after the start of adolescence. In other words, it is the span of life between adolescence and the early thirties which may be watched with the best prospect of detecting the first appearance of these lesions.

How quickly a lesion may appear in a lung which previously was healthy on X-ray examination is still not very clear. To answer this nearly accurately would require an X-ray examination of a group of healthy young people every week for a number of years; obviously, an objectionable undertaking. However, certain implications may be seen in our observations. For similar reasons we are not prepared to say much about the relation of the early lesion to recent primary infection. In contrast with young children a peculiarity in young white adults, who were tuberculin-negative, then became tuberculin-positive and still later developed pulmonary lesions, is the usual failure to demonstrate by X-ray a typical primary complex; visible enlargement of the regional lymph nodes usually is lacking. Consequently, because the frequency of tuberculin testing must be limited, it is seldom possible to judge clearly whether the lesion discovered is primary, or whether it represents an extension from the primary or an exogenous reinfection.

As to the pathological nature of the early lesion one must depend chiefly upon the interpretation of roentgenographic densities; and this must be done with considerable reservation. In a relative minority of instances the pulmonary field, which on previous examination was clear, contains a new, round, discrete, nodular shadow, usually less then a centimeter in diameter, which conforms with

[1] Bellevue Hospital, New York City.

that of a productive tubercle. But this appearance may be deceptive because it is known that the roentgenographic density of small exudative lesions at their start may have little of the collateral haze which is one of the signs of this type of reaction, that is, there may be a well defined border indicating the limitation of the inflammatory exudate within broncholobular walls rather than the periphery of a productive tubercle. The confusion is not so great in lesions more than a centimeter or so in diameter; first, because we know, the larger the size, the more likely is the process to be wholly or partly of an exudative lobular pneumonic nature, and second, because larger lesions usually cast shadows with soft hazy borders. At the autopsy of many chronic tuberculous subjects the reliability of these criteria is verified within certain limits by studying recent lesions of bronchogenic origin, the duration of which is fairly well known from antemortem observation. By this approach the conclusion is reached that most early lesions are predominantly exudative.

In practice one learns that age and race have an important influence. The younger the subject, the more likely is a newly developed lesion to be exudative, a feature which is somewhat more striking in adolescent girls than in boys, and in Negroes than whites. So many observations point this way that one is prompted to utter a dictum: Until careful observation proves otherwise, assume that a tuberculous lesion, newly developed in the lung of a previously healthy person, is an exudative infiltration and, therefore, potentially very unstable.

The term *infiltration*[2] is aptly applied to the exudative lobular pneumonic or bronchopneumonic lesion. Morphologically it has the same connotation now as it had when first used by Laennec to distinguish it from the tubercle. The distinction is fundamentally important because of the different potentialtities. Whatever the underlying cause may be, the productive (miliary or conglomerate) tubercle tends to follow a mild and indolent course, enlarging and undergoing caseation and excavation slowly, whereas the infiltration (gelatinous or gray) is much more labile, frequently spreading and breaking down rapidly. Similarly the infiltrate may become absorbed much more rapidly than the productive tubercle; or the serous and cellular elements at the periphery of the infiltrate may be absorbed while the liquefied caseous centre is excavated.

Sometimes, in retrospect, one may find in a previous roentgenogram a tiny focus which presumably may have been the precursor of the early infiltration, but, without a knowledge of subsequent events, the diagnosis of tubercle, rather than blood vessel, would have been highly imaginative, to say the least. Nevertheless, there is much to suggest that many or most recognizable early lesions are in reality extensions from preëxisting occult foci. What we call "early" applies only to that which is demonstrable. It is a relative term which once referred to the lesion initiating symptoms but now to that casting an identifiable roentgenographic shadow.

Knowing that exudative infiltrations inevitably change progressively or

[2] The term *infiltration* refers to the *process* by which the tissue is invaded by tuberculous inflammation, while the term *infiltrate* is used to indicate the lesion produced by the process.

retrogressively, we have paid particular attention to the later evolution of those discovered early. The dominant trend of extensive pneumonic infiltrations to caseation and excavation has been noted by clinicians generally. Small early infiltrations behave in a similar way, the one apparent difference being quantitative; central necrosis is the striking tendency. In fact, this is so common as to suggest that almost all, if not all, early lesions are caseous at the centre by the time they can be diagnosed by X-ray. The cavity, when present, is often so minute that it can scarcely be recognized in the roentgenogram; special techniques may be required. That the pinhead or pea-sized rarefactions usually denote excavation is verified by their later enlargement and, as a rule, by the demonstration of tubercle bacilli in the scanty sputum or in the gastric washings upon meticulous examination.

The behavior of the periphery of the early infiltration is conditioned largely upon the rate and extent of the central caseation, the apparent reason being that the former depends upon the rate of manufacture in and local diffusion of toxic substances from the latter. If caseation is minimal and sloughs out early, the peripheral exudate is likely to be absorbed rapidly, and the minute cavity may close promptly; secondary bronchogenic lesions are slight or absent. If caseation is rapid and extensive, peripheral extension is greater; when the liquefied matter is discharged into the bronchial tubes extensive—even lobar pneumonic—secondary lesions may result. If caseation is small or moderate in extent (usually not more than 1 or 2 cm. in cross-section) and becomes arrested with little or no ulceration into the bronchus, the peripheral exudate may be gradually absorbed and organized, encapsulating the cheesy residues; roentgenographically, these often have the appearance of so-called "round infiltrates."

The rate and succession of these changes vary greatly. At the start of our study the usual routine of making roentgenographic observations once a month or so was followed. Soon it was found that some lesions changed markedly in this interval. Now it is routine, upon discovering a newly developed lesion in a previously healthy person, to make the examination every week during the first one or two months. Occasionally an interval of several days is the limit. It has been discovered, especially in adolescent and young adult patients, that a cavity, 2 or 3 mm. in diameter, may appear within a week; an infiltration 1 cm. in diameter may double or triple its size in one to four weeks; an infiltration 1 to 2 cm. in diameter may abruptly discharge its liquefied caseous contents into the bronchi, thus inciting an acute tuberculous lobar pneumonia within two to four weeks. Some early infiltrations remain stationary for weeks or months, then rapidly change with excavation and numerous and extensive secondary lesions. The transition from the early lesion to advanced bilateral disease, in exceptional cases, is a matter of only a few weeks. Resolution, when it occurs, is slow. At first the peripheral exudate, perhaps quite serous, may be seen to absorb rapidly within several weeks, but as a rule the process slows as the core of the lesion is approached. In several months minute residues remain—almost naked caseous remnants which may be visualized as collections of myriad or-

ganisms, delicately imprisoned, waiting for some passing disturbance to spread them far and wide. Needless to state, the warm, fertile lung is ever receptive for the threatened dissemination. During the subsequent two years, approximately, circumstances decide whether wide destruction is initiated, whether the slow process of fibrous encapsulation may become competent and permanent, or whether an indecisive balance between the forces of destruction and repair leaves the lesions in that uncertain and sad state, known as chronicity.

For the clinician especially a most interesting observation is the lag between pathological morphological change and systemic effects. For example, upon first discovering an early infiltration the erythrocyte sedimentation rate usually is reported normal. During the subsequent few weeks a steady or intermittent extension of the lesion, perhaps with excavation, may occur without any coincidental change in this test. Then as the pulmonary involvement continues the sedimentation rate for the first time is accelerated; a few days or weeks later the initial fever may be detected. One may interpret this to mean that the diffusion of toxins must persist and reach a considerable level before the systemic effects are measurable by the ordinary clinical and laboratory tests. In some cases tubercle bacilli are discovered in the sputum before these effects are detected.

Certain implications may be seen in these observations. In all probability a tuberculous infiltration may develop in the lung within a few days to several weeks. That this may be the first demonstrable extension from a preëxisting occult focus cannot be denied.

When an infiltration is fresh, with only minimal central caseation, the possibility of resolution and complete healing is greater than it is at any subsequent phase of the disease. Conceivably, conditions would be more favorable if the small caseous core had been extruded, but this seldom occurs without some infection of the surrounding parenchyma.

The opportune time for securing maximal effects of treatment is in this early phase, preferably before there are any severe systemic symptoms and before secondary bronchogenic lesions have had time to develop. To wait for the lesion to give indubitable evidence of its "activity" usually means that the best opportunity for cure has been lost. Fortunately, this does not imply that an "arrestment" may not occur later. But, to accomplish the most for the patient, the fact must frequently be emphasized and well remembered that a small lesion, demonstrable only by X-ray and wholly symptomless, may be an early infiltration with serious and closely impending potentialities. Unless it is unmistakably fibroid, such small lesions at the start should be observed roentgenographically at weekly to biweekly intervals. Preferably, the patient should be on rest treatment while this is done. These conceptions have proved in our experience to be a sound basis of treatment with results surpassing any other scheme which we have tried. The experience seems to indicate that, if the conceptions could be applied generally, tuberculosis would seldom become the advanced and fatal disease with which, regrettably, we are so familiar.

SUMMARY

The behavior of the earliest lesions of pulmonary tuberculosis can be understood only by a systematic study of apparently healthy people among whom the disease may be expected to appear. The period of life between the start of adolescence and the age of thirty or thirty-five is the time during which most of these lesions first develop.

Most lesions of the early infiltration are of a predominantly exudative, lobular pneumonic character; this type of tissue reaction is most conspicuous in adolescents, especially in young girls and in Negroes. The assumption should be made, until well proved otherwise, that this type of reaction prevails, remembering that the roentgenographic appearance may be misleading.

The striking tendency of the early infiltration is to progress to the point of caseation and excavation. Close study demonstrates that such changes may be rapid; for example, a small lesion may enlarge, caseate, and slough out within a week or two, and given rise to extensive secondary bronchogenic lesions.

Usually, systemic effects, such as fever and an accelerated erythrocyte sedimentation rate, are not apparent at the time of the early infiltration and there is often a considerable lag in these effects while the lesion is advancing.

It may be inferred from our studies that the early infiltration may develop within a few days or weeks in the lung of a previously healthy person. There is reason to believe that in many or most instances there have been preëxisting occult foci which served as points of origin.

Treatment is most successful if it is based on these conceptions; usually advanced tuberculosis can be avoided.

SUMARIO

Sólo puede comprenderse el comportamiento de las lesiones más tempranas de la tuberculosis pulmonar mediante un estudio sistemático de sujetos aparentemente sanos, entre los cuales puede esperarse que se presente el mal. El período de vida entre el comienzo de la adolescencia y la edad de treinta o treinta y cinco años es la época en que la mayor parte de esas lesiones aparecen por primera vez.

En la mayor parte de las lesiones tempranas de la infiltración predomina la forma neumónica lobular exudativa; este tipo de reacción histológica es más notable en los adolescentes, y en particular en las jóvenes y en los negros. Hasta que se demuestre lo contrario, debe suponerse que existe esta clase de reacción, recordando que el aspecto roentgenográfico puede prestarse a confusión.

La tendencia sobresaliente de la infiltración temprana consiste en seguir avanzando hasta producir caseación y excavación. El estudio detenido demuestra que esas alteraciones pueden ser rápidas; por ejemplo, una lesión pequeña puede agrandar, casear y esfacelar en una semana o dos, y producir extensas lesiones broncógenas secundarias.

Por lo general los efectos orgánicos en forma de fiebre y de acelerada sedimentación de los eritrocitos no se manifiestan en el momento de la infiltración

temprana, y a menudo hay un retardo considerable en estos efectos mientras la lesión avanza.

Cabe deducir de nuestros estudios que puede presentarse infiltración temprana a los pocos días o semanas en el pulmón de un sujeto previamente sano, habiendo motivos para creer que en muchos o en la mayor parte de esos casos puede haber focos ocultos preexistentes que sirvieron de punto de origen.

El tratamiento da mejor resultado si se basa en estos conceptos, pudiendo por lo general evitarse la tuberculosis avanzada.

DIFFERENTIAL DIAGNOSIS IN PULMONARY TUBERCULOSIS

JAMES J. WARING[1]

The phrase "differential diagnosis" involves a discussion of the diagnostic features of one disease of primary interest and the signs and symptoms distinguishing it from the maladies with which it is most commonly confused. I shall, therefore, begin with the diagnosis of pulmonary tuberculosis.

When should the doctor suspect tuberculosis? Where should the doctor expect to find tuberculosis, that is, under what conditions or in what environment is tuberculosis commonly found?

The time to think of tuberculosis is when the patient first puts his foot in the door of the doctor's office. The specialist or expert in tuberculosis thinks of tuberculosis always first and continues to think of it until he has proven it is not present. Too often the general practitioner thinks of tuberculosis last. Let no doctor forget that tuberculosis may "crop up" any time, any place. By this I mean, it may appear at any age, in any home, in any occupation, in a word, in any environment. Wealth, social position, athletic records, even advanced years, a pious life and a "spotless" family history do not furnish immunity to tuberculosis.

"How can it be tuberculosis," says a distressed mother, "when we have never had a case in our family?" "How can it be tuberculosis," says the unhappy father, "the boy was full-back last year on his college team?" Well, it not only can be but it is tuberculosis! This dangerous notion that tuberculosis appears only where there is a family history of tuberculosis is a relic of the equally false doctrine that tuberculosis is, strictly speaking, hereditary. It disregards unrecognized tuberculosis in the home, for example, the numerous old people who suffer from tuberculosis under the guise of chronic bronchitis or "winter cough." It takes no account of the possibilities of infection from temporary boarders, servants, room-mates in school and college. It discounts fellow employees, even the "boss," as possible sources of infection. It takes no account of hazardous occupations. It takes no thought of marital tuberculosis!

On the other hand, I do not wish to imply that a family history of tuberculosis is not important. It conspicuously declares that serious opportunities for infection are or have been present. Bullet wounds are found in the firing line, arrow-heads where there have been Indians, ducks on the pond, larks in the meadow, tuberculosis where there has been or is tuberculosis—the environment is the thing! But whether the tuberculous hazards of that environment are obvious, discoverable by searching interrogation or undiscoverable by any means, *we must always suspect tuberculosis*! A negative family history does not throw a good medical attendant off guard; it does not exclude tuberculosis any more than normal physical signs or the appearance of good health exclude tuberculosis. A positive family history furnishes a diagnostic clue that must be followed with the greatest care.

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The environment may be directly dangerous because of the presence of tubercle bacilli or indirectly dangerous, first, because of a generally depressing effect upon the health, or second, because something in the environment specifically lowers the resistance of the lungs to tuberculosis. Among these hazardous occupations the most important are those which necessitate exposure of the worker to the inhalation of siliceous dusts. A history of such exposure, its duration and severity is of the greatest importance in diagnosis.

Pleurisy with effusion; ischio-rectal abscess: Besides a family history of tuberculosis, a history of contact with tuberculosis at home or at work, and a history of long exposure to siliceous dusts, it is important to question carefully for a history of nonpulmonary tuberculous conditions, for example, tuberculous cervical adenitis or conditions not infrequently of tuberculous origin, such as pleurisy with effusion and ischio-rectal abscess with its residual fistula-in-ano. Although the subsequent histories of 83 patients admitted to Trudeau with a history of pleurisy with effusions are surprisingly reassuring, 89 per cent were well and working after a four to twenty-five year follow-up, I would nevertheless view with alarm a young adult with this condition and I would follow closely over the years, with repeated semi-annual or annual physical examinations and X-rays films, the young adult with a history of such effusion. Examination of all pleural fluids should include: general appearance, specific gravity, cytology, staining for tubercle bacilli of sediment from centrifuged specimens, repeated cultures for tubercle bacilli and guinea pig inoculations. A specific gravity over 1.016, a lymphocyte count over 30 per cent suggest tuberculosis. A bloody effusion, if heart disease, neoplasm, cirrhosis of the liver can be excluded, strongly suggests tuberculosis. After the fluid has disappeared, X-ray films of the chest should be studied with the greatest care. If tubercle bacilli are not demonstrated in the pleural fluid by any method and if the X-ray film shows not even minimal parenchymal shadows the prognosis is excellent.

Every patient with ischio-rectal abscess should have his lungs checked at once and annually thereafter for some years. Not infrequently, ischio-rectal abscess and its sequel fistula-in-ano precede by a few years pulmonary signs or constitutional symptoms of pulmonary tuberculosis. So much for family and personal histories!

Symptomatology: Let it be said at the outset, active pulmonary tuberculosis may exist in the complete absence of symptoms, indeed in a person who looks and feels perfectly well. Since it is of vital importance to discover tuberculosis when it is minimal, at the very time when symptoms may be few or absent, how does the doctor have the opportunity to make a diagnosis and discover the disease this early? Unfortunately the doctor gets that opportunity all too infrequently. Most pulmonary tuberculosis is discovered in moderate or far-advanced stages, but some minimal disease is picked up by looking for it where it is most likely to appear, among student nurses, medical students, college boys and girls, employees of large corporations, family contacts with open cases of pulmonary tuberculosis. Student health clinics on the increase among schools and colleges in the United States and industrial clinics also on the increase will

catch some of these cases, but I would urge family physicians to make routine physical examinations and X-ray films of the lungs of all boys and girls of teen ages under their observation before letting these children return to school and college in the fall.

What are suspicious symptoms of pulmonary tuberculosis? In my opinion the most important are: chronic fatigue, loss of endurance, unusual irritability, loss of appetite, loss of weight, vague pains in the chest, fever and a rapid pulse, recurrent laryngitis, wheezing or faint purring or clicking sounds in the chest during inspiration, cough, greenish, yellow or bloody expectoration and haemorrhage. Not one of these symptoms is pathognomonic of tuberculosis, but combinations of them should arouse suspicion of tuberculosis.

Fatigue; irritability: One patient may have very pronounced symptoms with minimal tuberculosis; another no complaints whatsoever with moderately advanced disease. I would emphasize the importance of chronic fatigue and loss of endurance as important symptoms. The sense of fatigue associated with pulmonary tuberculosis is a deadly thing. It needs to be experienced to be appreciated. It clings relentlessly by day weighting the feet with lead and the back with heavy burdens. It goes to bed with its victim at night and gets up with him in the morning. It is linked closely with loss of endurance, irritability and loss of appetite. Curiously enough, every mother knows what the physician sometimes forgets, that peevishness and irritability are frequently due to fatigue or infection. "The baby is fussy! He missed his nap to-day," says the young mother, a bit apologetically. Change of disposition is not infrequently mentioned by the pediatrician as an early sign of this or that infectious disease, especially tuberculous meningitis. It is sadly neglected as a sign of illness or poor health in grown-ups! I am convinced that much ill-temper that is not ingrained is based on fatigue or what we loosely call toxaemia. Some of this irritability can be passed off with a dose of castor oil or a brief rest in bed. Just this year, I saw a young woman, thirty-five years of age, obviously but not very sick with an acute upper respiratory infection. "She has been so cranky the last few days, I gave her a dose of castor oil which always straightened her out as a child when she got fussy," said her mother.

A middle-aged man with pulmonary tuberculosis told me pathetically that, during the year preceding recognition of his disease, his usual genial disposition had changed so decidedly that his friends rebuked him for being "so damn cranky." In young people great weariness and ill temper that do not pass with a week-end's rest in bed urgently require investigation. Chronic fatigue begets loss of appetite and continued loss of appetite begets loss of weight. Fatigue, a weariness affecting the legs especially, is particularly noticeable when the afternoon temperature creeps above normal.

Fever: The main characteristic feature of fever in tuberculosis is its fiendish persistence. The diurnal variation of mouth temperature in a normal person is less than one degree with a high point of 98.6° F. or just below in the afternoon or early evening. The morning temperature before arising and before the morning toilet in a room temperature of 65° to 70° F. is just below 98° F. Not

uncommonly the fever of early tuberculosis pushes the morning and afternoon readings up one-half to one degree. The morning temperature, therefore, would start at 98.6° F. or just below and the afternoon reading would be 99.6° F. or just below. This type of temperature curve is much more significant in men than in women in whom it has to be differentiated from the normal premenstrual rise of temperature. The trend of the temperature over a week or ten days is the important thing and not the single reading. Every patient should have his temperature taken every time he comes to the doctor's office. When tuberculosis is suspected, the patient should take his temperature according to instructions four times daily for a week and keep a record of it to show the doctor. An elevated pulse rate without fever may be found early; when both are elevated, the temperature following rest in bed may return to normal long before the pulse rate does.

Pleuritic pains: Pains in the chest in pulmonary tuberculosis vary from the stabbing pain with every breath of acute pleurisy to a dull ache or sense of oppression more or less localized, front or back. Pain in the chest demands investigation by physical examination, fluoroscopic examination, X-ray films of the lungs and occasionally by bronchoscopic examination.

Bronchial clicks: Growing appreciation of the importance of tracheobronchial tuberculosis has led specialists in tuberculosis to pay more attention to the little sounds in the chest audible usually to the patient, and not infrequently to him only, on reclining. These sounds can be heard by the examiner with his ear close to the patient's open mouth or by the examiner when he holds the bell of his stethoscope close to the patient's open mouth as the patient breathes. I refer less to the wheeze characteristic of bronchial stenosis than to the faint clicking or purring sounds best heard by the patient himself and often puzzling to him because they seem difficult to locate. Sometimes they disappear by change of position or after slight cough. When they occur in the absence of manifest acute or recent acute respiratory infections, they require investigation. Normally during waking moments, ventilation of the lungs proceeds noiselessly; in the presence of tuberculous infection, a little sticky mucopurulent material accumulates in, perhaps fills one or more small bronchi or seals the mouths of small bronchi with a film as soap makes a film over a blow-bubble pipe. During inspiratory dilatation of the bronchi, air sucked past or through these obstructing bits of mucus makes a faint clicking sound or many faint clicking sounds. If many bronchi are filled with sticky mucus, the sounds are numerous and heard on both inspiration and expiration and become more or less purring. If the bronchus is partially stenosed, the sounds become definitely wheezing, which leads me to say, it is just as well to bear in mind that all is not asthma that wheezes! Somewhat similar sounds are heard in practically all chronic pulmonary disorders with mucopurulent discharge. The sound is more frequently heard in tuberculosis, is more sticky in character, is not uncommonly present when the patient denies expectoration. It indicates nothing more than a little mucopurulent material in the bronchi but *that* is enough to demand investigation.

Physical examination: I would stress the fundamental importance of exam-

ining the patient with the chest completely bare in a good light out of bed. Any examination of the patient in bed is unsatisfactory and not to be relied upon for anything but the more obvious signs. Auscultation should be carried out only after the patient has been carefully instructed to exhale, cough and then inhale and has demonstrated to the satisfaction of the examiner that he understands what he is to do. Years ago, Lawrason Brown said that the difference between the specialist in tuberculosis and the general practitioner lay in the fact that the specialist makes the patient inhale after an expiratory cough when examined and the general practitioner does not. To this I would add, the specialist thinks of tuberculosis first, the general practitioner last!

A fluoroscope should be an indispensable part of the equipment in every doctor's office. After only moderate experience very little early tuberculosis will be missed by a careful examiner. No examination of the chest is complete without X-ray pictures of the lungs, which should include a good lateral as well as the usual postero-anterior views. Although tuberculosis is commonly found in the upper thirds of the lungs, it can be confined to the base of one lung.

Finally, a complete and accurate diagnosis of tuberculosis is dependent upon the demonstration of tubercle bacilli in the sputum. Just as the sputum in pneumonia has a quite characteristic appearance, so the sputum in tuberculosis is typical. Very early in acute stages it is almost greenish, later it is stringy yellow mingled with clear mucus and saliva. In suspected cases no examination of the sputum for tubercle bacilli should be considered negative until tests have been made not only by direct smear and concentration methods but by gastric lavage, culture and guinea pig inoculation, repeated as often as the clinical experience of the examiner would demand. In a few puzzling cases, I have been successful in demonstrating tubercle bacilli in the direct smear made at the time of bronchoscopic examination when the sputum smears previously had been repeatedly negative.

The general practitioner does not make sputum examinations often enough; furthermore, he is too easily satisfied with the negative examination by direct smear. Every specimen of sputum sent to any hospital, private, municipal or state laboratory for typing for pneumococcus should be stained for tubercle bacilli. In other words, every patient suspected of having pneumonia should also be suspected of having tuberculosis. The doctor should say to himself: "It looks like pneumonia but I do not want to overlook tuberculosis."

Haemoptysis, haemorrhage: In tuberculosis, blood in the sputum may vary from microscopical amounts to flecks of bright blood, streaks of bright blood, sputum thoroughly impregnated with blood and rusty in appearance, bright blood in small amounts with very little or no admixture of mucous or mucopurulent material. Bright blood may vary in amount from a dram to an exsanguinating haemorrhage. Always and everywhere, red has been the signal of danger. Bloody sputum has roused many a man to the realization that something was seriously wrong with his chest. Cough and expectoration are always worth the notice of the medical attendant but bloody sputum clamors for investigation! It is well to know that the very first symptom of pulmonary tuberculosis may be more or less severe haemorrhage from the lungs.

Some years ago Lawrason Brown and Heise suggested five criteria for the diagnosis of pulmonary tuberculosis. They are:

1: A history of pleurisy with effusion.
2: Expectoration of a dram or more of blood.
3: Râles above the second rib and third dorsal spine.
4: X-ray film showing parenchymal shadows in the same region where râles are heard.
5: Sputum positive for tubercle bacilli.

When all these five criteria are missing, pulmonary tuberculosis can be excluded. Haemoptysis or pleural effusion justify a strong suspicion of tuberculosis. Both haemoptysis and pleural effusion, whether coincident or not, almost surely indicate tuberculosis. Râles not supported by X-ray shadows in the corresponding portions of the lung are inconclusive but demand further investigation. In the absence of symptoms, shadows on the X-ray film, particularly in the upper one-third of the lung field, for accurate diagnosis require great skill of interpretation and wide clinical experience.

The diagnosis of pulmonary tuberculosis can be made best by the man who knows the history of his patient, has examined him carefully and has the requisite experience for accurate interpretation of the X-ray film. The family physician ought to be the best man to correlate history, symptoms, physical signs, laboratory studies and X-ray pictures. As a matter of fact, 75 per cent of the diagnoses of pulmonary tuberculosis are made by the general practitioner.

Tuberculin tests: The diagnostic value of the tuberculin test can be summed up very briefly. Except for the rare occasions when the test is negative in far-advanced pulmonary tuberculosis with the diagnosis not in doubt and the patient moribund, the test is practically always positive in the presence of active pulmonary tuberculosis. On the other hand, a negative test in a manifestly sick person is very strong evidence against the presence of active pulmonary tuberculosis.

Active pulmonary tuberculosis has been seen to develop rapidly after the first appearance of a positive tuberculin test. On the other hand, there is no adequate proof of the development of active pulmonary tuberculosis without the tuberculin reaction becoming positive. These facts are of great clinical significance.

Differential diagnosis: Pulmonary tuberculosis has to be differentiated from the following maladies: acute lobar pneumonia, acute or chronic bronchopneumonia, lipoid pneumonia, acute or chronic bronchitis, bronchiectasis, abscess of the lung, pneumonoconiosis, foreign body in the lung, cystic disease of the lung, tumor of the lung, heart disease, pulmonary embolism, pulmonary infarct, fungus disease of the lung, especially coccidioidomycosis, psychoneurosis, thyrotoxicosis, neurocirculatory asthenia or "soldier's heart."

It will be noted that all of these diseases, except the last three and the circulatory disorders, are characterized by purulent sputum which may be bloody. Pulmonary infarction and pulmonary embolism simulate acute pneumonia as well as acute tuberculosis of the lungs. I have never seen haemorrhage in simple acute or chronic bronchitis, but haemorrhage occurs in all the others.

All of them have fairly characteristic histories, symptoms, physical signs and X-ray pictures. In the acute pneumonias the symptoms and the abnormal physical signs disappear in a week or two; the changes revealed by the X-ray may linger much longer. All these signs are certainly short lived compared with tuberculosis. Chronic bronchopneumonia, especially that due to the Friedländer's bacillus, bronchiectasis, abscess of the lung, cystic disease of the lung, fungus disease of the lung are most apt to cause confusion in diagnosis. In chronic Friedländer's bacillus infection of the lung, the sputum is commonly a tenacious, brick-red emulsion of blood and mucus. Because of the frequent involvement of the upper lobes with much fibrosis and cavity formation, the physical signs and X-ray picture of this form of pulmonary disease may strongly resemble tuberculosis. Expert bacteriological study of the sputum is helpful in making the diagnosis. This much may be said in favor of the tubercle bacillus, its presence in the sputum is a positive indication of tuberculous disease of the lung. As much cannot be said for the aetiological significance of some other organisms which may be isolated from the sputum. In other words, Friedländer's bacillus in the sputum does not necessarily mean Friedländer's bacillus infection of the lung; fungi in the sputum do not necessarily mean fungus disease of the lung.

Coccidioidomycosis: Although coccidioidomycosis of the lung is very rare outside of California and Arizona, the disease bears such a remarkable resemblance to tuberculosis, pathologically, clinically and radiologically, that it is important to be familiar with its manifestations.

Like the tubercle bacillus, the fungus *Coccidioides immitis* produces localized and generalized disease of acute, subacute or chronic nature. It shows a predilection for the lungs and lymph nodes but also attacks skin, bones and nervous system producing clinical pictures simulating tuberculous infections. Any of the local forms may become generalized and involve any or all of the organs and tissues of the body, except the intestinal tract.

Inhalation of the fungus produces an acute pneumonic process in the lung with moderately severe constitutional symptoms, cough, sputum occasionally bloody and rarely serous or purulent pleural effusions. Like primary tuberculosis of the lungs, this first infection is usually a benign affair, shortly subsides and both the abnormal physical signs in the chest and the radiological evidences of infiltration of the lung and involvement of the hilar lymph nodes disappear. Residues of this first infection may persist in the lungs or lymph nodes and may play an important part in subsequent recrudescences of the disease. The analogy to tuberculosis is further emphasized by the fact that shortly after infection skin hypersensitivity develops to an extract of the causative organism. Like the tuberculin reaction this hypersensitivity may persist. An attack of erythema nodosum in a few days or a few weeks after subsidence of this primary phase of the disease is characteristic and furnishes an important means of differentiation from tuberculosis.

In a recent report on 13 cases of pulmonary coccidioidal infection, W. A. Winn says coccidioidal cavitation is a relatively benign affair which develops almost

exclusively during or shortly after the primary stage of pulmonary infection and not during the later "reinfection stages" as in pulmonary tuberculosis.

However, others have reported a much more serious granulomatous process which develops later in the lungs. The physical signs and X-ray changes are typical of tuberculosis. The patient presents the picture of a progressive pulmonary disease with severe constitutional symptoms, emaciation, much fibrosis, cavity formation, pleural effusions, multiple bone involvement, numerous sinuses and frequently a terminal meningitis.

When the organism enters the body through the throat it produces a clinical picture resembling tuberculous cervical adenitis.

Differentiation from tuberculosis may be secured by attention to the following points:

1: Coccidioidal granuloma should be suspected in any person from the endemic areas in the San Joaquin valley in California or Arizona with chronic pulmonary disease.
2: Examination of the sputum in the one instance will show tubercle bacilli, in the other, *Coccidioides immitis.*
3: The skin test with coccidioidin has a high degree of diagnostic accuracy.
4: A high eosinophilia suggests coccidioidomycosis.
5: Multiple bone lesions are more common in coccidioidal granuloma than in tuberculosis!

Bronchiectasis: In bronchiectasis a history of copious expectoration since childhood is characteristic. In no other disease of the lung is there such a remarkable disproportion between the large quantity of sputum and the few physical signs and lack of severe persistent constitutional symptoms. Clubbed fingers are more common in this malady than in chronic tuberculosis. The diagnosis is clinically easy but should be made in detail by complete bronchograms of the lungs, with X-ray pictures in lateral as well as postero-anterior views. Bronchoscopic examination should always be made.

Carcinoma of the lung: As to endobronchial carcinoma of the lung, the salvation of the patient depends upon early diagnosis. Suspicious symptoms that should cause the patient to seek medical advice are cough, expectoration, occasionally bloody sputum, a wheeze, vague pains in the chest, shortness of breath. Physical signs and symptoms suggesting partial bronchial obstruction demand prompt, sometimes repeated bronchoscopic examination. The diagnosis, early before complete bronchial occlusion, can be made only by bronchoscopic examination, including perhaps biopsy.

Information derived from expert bronchoscopic examination is frequently essential to a diagnosis of certain nontuberculous conditions of the lung. When tubercle bacilli are absent from the sputum after searching scrutiny by the most up-to-date methods, tuberculosis can usually be excluded. A reliable negative tuberculin test always assists in excluding tuberculosis.

In "soldier's heart" cough and expectoration are usually missing. Such sputum as may be present is negative for tubercle bacilli. The tuberculin test may be negative, the X-ray film shows no unmistakable evidence of tuberculosis.

SUMMARY

1. Wealth, social position, athletic prowess, a pious life and a "spotless" family history do not furnish immunity to tuberculosis.

2. The specialist thinks of tuberculosis first, the general practitioner thinks of tuberculosis last.

3. The specialist always makes the patient inhale after an expiratory cough during the chest examination; the general practitioner is learning to do so.

4. The appearance of good health and a feeling of well-being do not exclude pulmonary tuberculosis.

5. Normal physical signs do not exclude pulmonary tuberculosis.

6. Although symptoms usually run parallel with the severity of the disease, it is well to remember that conspicuous symptoms may be present with minimal tuberculosis and no symptoms whatsoever present with moderately advanced tuberculosis.

7. No examination of the chest is complete without an X-ray film of the lungs.

8. Cough and expectoration are always worth the notice of the medical attendant, but bloody sputum clamors for investigation.

9. Tracheobronchial tuberculosis and tumors of the bronchi occasionally masquerade as simple asthma.

10. Bronchoscopic examination is most useful in the diagnosis of nontuberculous pulmonary conditions.

11. The general practitioner is too easily satisfied with one negative sputum examination.

12. Every sputum sent to the laboratory for typing of pneumococcus should also be examined for tubercle bacilli.

13. In the presence of active pulmonary tuberculosis, the tuberculin test is practically always positive.

14. In a manifestly sick person, a negative tuberculin test almost certainly excludes tuberculosis.

15. The medical student, trained nurse, young doctor or any member of hospital or sanatorium personnel converting a negative to a positive tuberculin test under observation, urgently requires examination and reëxamination over the next few years.

16. In the presence of manifest heart disease, especially mitral stenosis, a diagnosis of pulmonary tuberculosis based upon haemoptysis or haemorrhage, shortness of breath and a fast pulse, should be made with caution.

17. The presence and the extent of bronchiectasis can be accurately determined only by bronchography.

18. Not infrequently a differential diagnosis of pulmonary disease can be made only after the lapse of time well spent in making repeated chest examinations, repeated X-ray examinations, one or more bronchoscopic examinations, repeated sputum examinations, including culture, gastric lavage and guinea pig inoculation.

SUMARIO

1. La riqueza, la posición social, el vigor atlético, la vida piadosa y una vida familiar inmaculada no crean inmunidad a la tuberculosis.

2. El tisiólogo piensa en la tuberculosis primero; el médico general en último lugar.

3. El tisiólogo hace siempre que el enfermo inhale después de una tos expiratoria durante el examen torácico; el médico general apenas está aprendiendo a hacerlo.

4. El aspecto de buena salud y la sensación de euforia no excluyen la tuberculosis pulmonar.

5. Los signos físicos normales no excluyen la tuberculosis pulmonar.

6. Aunque los síntomas suelen guardar relación con la gravedad del mal, conviene recordar que pueden existir en forma notable con una tuberculosis mínima, y hasta faltar en una tuberculosis moderadamente avanzada.

7. No hay examen torácico completo sin una roentgenografía de los pulmones.

8. La tos y la expectoración merecen siempre atención de parte del médico, pero un esputo sanguinolento pide a gritos investigación.

9. La tuberculosis traqueobronquial y los tumores de los bronquios suelen a veces enmascararse en forma de asma simple.

10. El examen broncoscópico resulta de la mayor utilidad en el diagnóstico de las neumopatías no tuberculosas.

11. El médico general se da por satisfecho sin razón con un examen negativo del esputo.

12. Todo ejemplar de esputo enviado al laboratorio para la clasificación de los neumococos debe también ser examinado en busca de bacilos tuberculosos.

13. En presencia de tuberculosis pulmonar activa, la reacción a la tuberculina es casi siempre positiva.

14. En una persona manifiestamente enferma, una reacción negativa a la tuberculina excluye casi seguramente la tuberculosis.

15. El estudiante de medicina, la enfermera avezada, el doctor joven o cualquier miembro del personal de un hospital o sanatorio, en el cual una reacción negativa a la tuberculina se convierte en positiva mientras está en observación, necesita con urgencia examen y reexamen en los próximos años.

16. En presencia de cardiopatía manifiesta, y en particular estenosis mitral, debe hacerse con cautela el diagnóstico de tuberculosis pulmonar basado en la hemoptisis o hemorragia, disnea y taquicardia.

17. La presencia y extensión de la bronquiectasia sólo pueden determinarse con exactitud por medio de la broncografía.

18. Bastantes veces sólo puede hacerse un diagnóstico diferencial de afección pulmonar después de algún tiempo bien aprovechado en verificar repetidos exámenes torácicos, repetidos exámenes roentgenológicos, uno o más exámenes broncoscópicos, repetidos exámenes del esputo, incluso cultivos, lavados gástricos e inoculación en el cobayo.

PHYSICAL PRINCIPLES IN PNEUMOTHORAX[1,2]

MAX PINNER AND AARON E. MARGULIS[3]

INTRODUCTION

The oustanding milestones in the development of pneumothorax treatment are technical refinements, clarification of indications and contraindications and general clinical judgment in its application, greatly enhanced by improved roentgenological interpretation. But a thorough understanding of the pertinent principles have badly lagged behind. This appears particularly true in regard to physical forces that are operative in pneumothorax and pulmonary collapse. It is probably rather the rule than the exception that proficiency of knowledge and technical skill are associated with a lack of interest—and therefore of understanding—for the simple physical forces on which (so frequently unbeknown to the therapist) the entire treatment is based. The meaning of such simple phenomena as intrapleural pressures, static and dynamic, changes in pulmonary volumina, composition of pneumothorax gases, elastic properties and varying elastic stresses of lung and surrounding structures are all too frequently not only misunderstood, but still more frequently not even questioned. That this state of affairs exists is shown by many curious statements in modern literature and particularly in verbal discussions and by the dearth of simple clarifying statements in pertinent textbooks.

It needs hardly be explained that a fuller and clearer understanding of the fundamental physical phenomena will help to improve the practical application of pneumothorax. For this reason, it seemed to us that a brief—and necessarily incomplete—exposé of the physical principles involved in pneumothorax may be justified.

The lung may be visualized as a honeycombed sack which, in the human, occupies two noncommunicating spaces bounded by the thoracic cage, the diaphragm and the mediastinum. When removed from the body the lung is smaller in volume than the space it occupies *in vivo*. In the body, therefore, the lung is distended and subject to elastic stresses. Moreover, during life the lung functions as a bellows whose volume varies continuously in the act of ventilation. It is hence subject to continuously varying elastic stresses. The elastic properties of the lung have been subject to study for many years, but there is a surprising dearth of unequivocal data relative to the elastic moduli of lungs at different ages, conditions of disease, etc. Many of the data are of indirect derivation, and many of them are culled from postmortem material which, it is now realized, is unreliable, since changes in pulmonary elasticity occur rapidly after death, and the vascular tree, which importantly influences

[1] This is the major part of a chapter prepared for the Handbook of Medical Physics, edited by Otto Glasser, now in preparation for the Year Book Publishers, Inc., Chicago.

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pulmonary elasticity is no longer in a state comparable to *in vivo* conditions. In general, it may be stated that the coefficient of elasticity is small, that is, small stresses produce relatively large deformations. Within physiological limits, normal lungs exhibit perfect elasticity (Cloetta (11)), that is, deformation (distension) is proportional to stress and there is no appreciable "set." This is not true in certain pathological conditions which have been investigated (Christie and McIntosh (8) in emphysema, heart failure).

It is the purpose of this paper to discuss the physical factors involved in pneumothorax therapy. During pneumothorax therapy the lungs function under altered stresses with modified dynamics, associated with changes in total pulmonary volumina and its subdivisions (complementary, tidal, reserve and residual air).

Therefore, the discussion must include: the method of collapse by pneumothorax, apparatus used, the altered dynamics and the effects on ventilation and pulmonary volumina.

The most important field for the application of pneumothorax therapy is, of course, in the treatment of pulmonary tuberculosis, whose healing, according to empirical observation, is frequently enhanced by collapse measures. A completely satisfactory explanation for this effect is not agreed upon, but certain effects of collapse therapy are well understood and will be mentioned later.

HISTORICAL NOTE ON PNEUMOTHORAX THERAPY

The basic rationale of collapse treatment is the clinical observation of the beneficial effects of massive pleural effusions on pulmonary tuberculosis. Pneumothorax was first systematically applied by Forlanini (28). He—as well as some forerunners in theory and his contemporaries in practice—believed that a diseased lung, immobilized by maintaining a pneumothorax with markedly positive pressure, will heal because of functional rest. In the further development of pneumothorax treatment, there is only *one* more really fundamental step, and this is the recognition by Ascoli in 1912 (5) that partial pulmonary collapse by subatmospheric intrapleural pressures produced better therapeutic results. All the other many innovations and improvements that have been added since Forlanini's time are modifications and technical refinements. Throughout the historical development of pneumothorax treatment, animal experimentation, physiological observations and a rational application of the physical laws concerned lagged behind the practical clinical use; this situation explains many misconceptions.

Some of the basically important measurements and experiments regarding intrapleural pressure in relation to ventilation were made in the study of the elastic properties of the lung. Such studies started with Carlson (1820). Christie and McIntosh (8) have reviewed the historical development.

METHODS USED IN THE STUDY OF VENTILATION

Spirometry

A description of the main apparatus used in measuring total ventilatory function is found in Cournand *et al.* (15). Since pneumothorax therapy is in most,

though not in all instances a unilateral procedure, it became important to use devices for the measurement of the ventilating and respiratory function of each lung separately.

Bronchospirometry

Jacobaeus in 1932 (26) first measured the ventilation of the two lungs separately through a double-channeled bronchoscope which permitted recording and analysis of inspired and expired air separately for each lung. This fundamentally important method was made considerably easier by the introduction of a soft rubber bronchial catheter (Gebauer (20), Zavod (44)).

Our own experiences with bronchospirometry in Montefiore Hospital are based on more than 250 examinations, the majority of which were done with reference to collapse therapy. The catheter for bronchial intubation used in our studies is described by Zavod (44) (figure 1). It is made of soft latex rubber, 55 cm. long. It has two channels, the bronchial extending over the entire length of the catheter, the tracheal being 9 cm. shorter. Following careful anaesthesia of the upper respiratory tract, the bronchial end of the catheter is introduced under fluoroscopic control into the left main bronchus. (For position of the catheter see figure 2.) The left bronchus is preferred because it is considerably longer between carina and upper lobe bronchus than the right; hence the likelihood to occlude the upper lobe bronchus is lessened. The two thin rubber bags just above the bronchial and tracheal openings of the catheter are inflated through their capillary channels, so as to occlude the left main bronchus and the trachea. These capillary channels are connected with mercury differential manometers and a pressure of about 60 to 180 mm. mercury is maintained which insures air-tight closures. At these pressures, minimal oscillations are seen, indicating inspiratory bronchial dilation and expiratory bronchial constrictions. Through the two separate channels, air from the right and left lung can be measured by the ordinary spirometric set-up in duplicate. The finer—and most important—details of the technique are described by Zavod.

Pneumothorax Machines

These include devices for induction or refilling of pneumothoraces and for the sampling of pneumothorax gases. The latter, although little used, can give valuable information as to the size of the pneumothorax space and the presence of bronchopleural fistulae; they have been used to study the composition of pneumothorax gases and the rate of their absorption.

The apparatus needed for the induction or refilling of a pneumothorax must (*1*) permit the introduction of a measured quantity of gas and (*2*) provide for the measurement of intrapleural pressure. These measuring devices also function as oscillometers for locating the pleural space.

Additional refinements proposed are devices for warming and filtering the gas, provision for reversal of air flow so that gas or fluids may be removed from the pleural space, recording devices for permanently recording the intrapleural pressure, and gas generating devices or tanks.

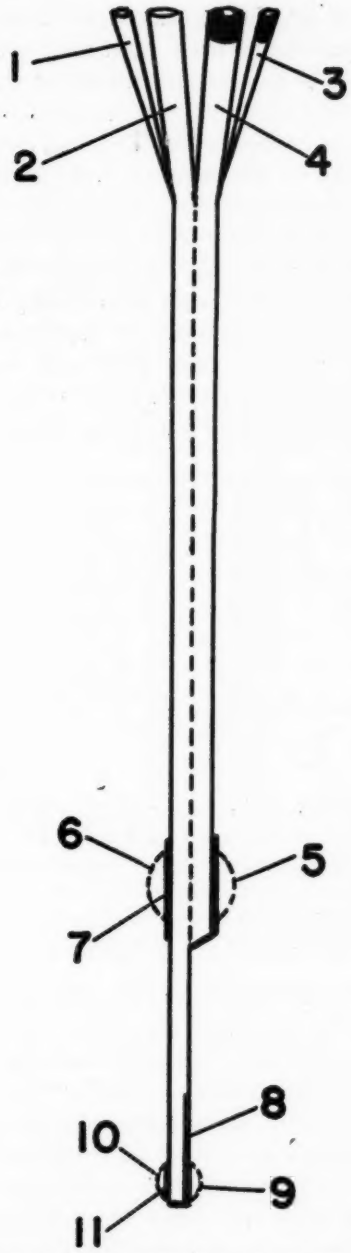


FIG. 1. Structural drawing of the bronchospirometry catheter.

Figures 1 and 2 are reprinted from the Journal of Thoracic Surgery (Wm. A. Zavod, 1940, *10*, 27) with the kind permission of the Editor, Publisher and Author.

Numerous apparatus have been devised for performing these simple functions, each designed to provide real or fancied advantages in the way of ease of opera-

tion, rigor of control, fool-proofness, ease of maintenance, compactness and portability. Many devices have been needlessly complicated, others oversimplified. The evolution of the modern machines has been exhaustively reviewed by Davidson (18) and need not be reiterated here.

A pneumothorax machine embodies the following parts:

A. *A reservoir:* This may be the chamber of a piston, a bellows or any container. The size of the reservoir determines the size and hence the portability of the machine. Since a refill may involve the introduction of up to 1,000 cc., several solutions have been proposed. Either the chamber is made initially quite large or some provision is introduced whereby it may be conveniently recharged during the treatment or between treatments (continuous reversal machines), that is, machines of unlimited functional capacity.

B. *A driving force:* In a few early models the air or gas was allowed to flow into the pleural space under the differences in tension between gas under atmospheric

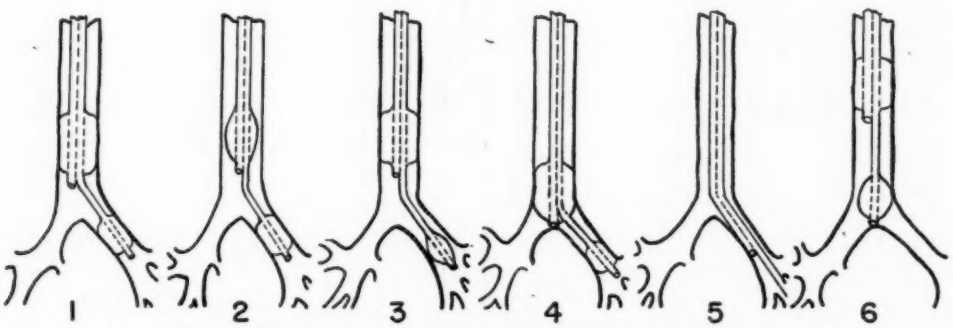


FIG. 2. *1:* Correct position of the catheter in the trachea and left bronchus. *2:* Tracheal bag underinflated. Leakage of air from the right lung. *3:* Bronchial bag underinflated. Leakage of air from the left lung into the tracheal channel carrying air from the right lung. *4:* Catheter too far down. Obstruction of the tracheal channel. *5:* Catheter too far down, tracheal and bronchial channels in the left bronchus. *6:* Catheter not down far enough, left bronchus not entered, obstruction of left bronchus.

pressure and that of the pleural space. But practically all modern machines have some arrangement to accelerate this flow. Since the desideratum is a relatively slow flow so that absolute control is available at all times, this entails a driving force of but a few centimetres of water. The devices designed for the displacement of the air into the chest comprise hydrostatic machines, that is, those that employ the gravitational force of a column of liquid to displace the gas (these are the most common types in use, for example, Davidson, Floyd-Robinson); those that employ the compression of the gas by piston, pump, rubber bulb or bellows (Bethune, Zavod) without a liquid for gas displacement. Some machines employ a combination of these.

C. *Manometer:* There have been employed mercury, water and aneroid manometers, the two former with closed and open arms. Two considerations are important, the conducting system and the intrinsic characteristic of the measuring device, problems common to all manometry. The rubber tubing

connecting the manometer and the intrapleural space must not be of excessive capacity, for a large dead space will introduce significant errors, particularly if the intrapleural pressure is much greater or less than atmospheric. The bore, of course, influences the characteristics of the system in relation to lag due to resistance of the flow in the air column. This is of more importance in the study of the dynamics of intrapleural pressure than in static measurements at preselected points. The limiting factor is the bore of the needle or trocar in the chest wall. A one millimeter bore in the needle or trocar is ample for the measurements of the fluctuation of intrapleural pressure, although a bore of 3 mm. is an advantage when time relationships are being studied. The rubber tubing need not be larger than 3 mm. in bore, and up to 100 cm. in length. For quantitative measurements of the fluctuation of intrapleural pressure the water manometer is the instrument of choice, although aneroids are also quite serviceable. Optical registration is cumbersome, calibration must be precise, and its use is restricted to research where time relations are being studied. Water manometers, although subject to both lag and overswing, are entirely suitable for clinical manometry, the former not being of moment and the latter of negligible practical degree. Where permanent records are desired, properly fitted tambours with writing points or optical methods may be used. The range of any sensitive water manometer is limited to 20 to 30 cm. of water. This is sufficient for registration under the usual conditions of initial or late pneumothorax. Under some conditions or in following the changes in vital capacity determinations, manometers with greater range are required. Mercury manometers may be employed, or water manometers in series. Open-tube manometers are most currently used. A word of warning must be introduced regarding scales used. In some earlier models centimeter scales were attached to each manometer arm and it became the custom to note only the scale reading of one arm, which of course is only half of the pressure difference. There is no rationale for this practice and it should be avoided. In later models the scale on one arm is frequently doubled so that by a single reading the pressure difference is ascertained. It has become a convention to report plus or minus "centimeters of water"—meaning the hydrostatic pressure of that many centimeters of water greater or less than the prevailing barometric pressure. Negative pressures have an algebraic but not a physical sense, and if the convention is kept clearly in mind certain inept physical statements can be avoided. In some models the manometer can be kept continuously in circuit, although their readings have no significance while the gas is flowing into the chest. In other models they are "cut in" by manipulation of stop-cocks at selected intervals.

D. *Accessory devices:* Devices for warming the gas are not utilized in current models, this refinement not proving necessary. The specific heats of gases are low compared to body tissues, and the gases are quickly warmed in the pleural space, entailing however some pressure and volume changes (see below). Filtering devices are always employed, usually consisting of a loose cotton plug through which the gas is passed. Stop-cock or other arrangements enabling reversal of the system, that is, the removal of pleural gas (in spontaneous pneumothorax)

or of exudates are very helpful. For further details about pneumothorax apparatus see Davidson (18).

Apparatus for Studying Pleural Gases

Devices for the sampling of pneumothorax gases are occasionally used to study pneumothorax gases and to determine the presence of bronchopleural fistula. The apparatus required is that commonly used in gas analysis, that is, some modification of the Haldane machine, fitted for the determination of oxygen and carbon dioxide and gas sampling tubes of the Bailey and Haldane type. Since one must also know the intrapleural pressures, these may be used in conjunction with the manometer of a pneumothorax machine. This measurement, however, "contaminates" the intrapleural gases, if determined prior to sampling, while sampling changes the pressure. Matsuzawa (31) (see also Ciaglia (10)) designed an apparatus (a Haldane tube with an incorporated manometer) which enables pressures to be estimated with a change in the pneumothorax volume of less than 0.25 cc. and a contamination of the pneumothorax gas with less than 0.04 cc. of atmospheric air (31).

PHYSICS OF THE PNEUMOTHORAX SPACE

Manometry and Intrapleural Pressures

It must be realized that intrapleural pressure measurements are not only observations made to elucidate pneumothorax therapy but are observations of real physiological significance. Normally the pleural leaves are in apposition, their contiguous surfaces moistened by a minimal amount of fluid. By intrapleural pressure is understood the tension on the surface of the lungs and on the parietal pleura. The condition existing during the suspension of ventilation is termed "static intrapleural pressure" and that during respiratory movements "dynamic intrapleural pressure." During respiration the intrapleural pressures are continuously varying functions with small plateaus during the momentary inspiratory and expiratory pauses. They are measured by introducing a bubble of air between the pleural leaves, this bubble of air acting as a tonometer and attaining a pressure in equilibrium with its surrounding walls. A needle in this bubble of air is connected with the manometer which records its static or dynamic pressure. As in all physical measurements the act of taking the measurement introduces a disturbance that changes the thing measured. Theoretically, every molecule of air introduced changes the volume of the pleural space, changes therefore the elastic stress of the lung and so alters the intrapleural pressure. The smaller the initial amount of air introduced, the closer does the measurement approach the actual measurement of normal intrapleural pressure, so that, theoretically, the figures approached asymptotically by decreasing amounts of air in the measuring bubble are the "true" intrapleural pressures. Practically, the introduction of 20 to 40 cc. of air produces at most a pressure increase of 0.5 to 1 cm. of water in the absence of pleural adhesions. It is not customary to attempt correction factors. In making intrapleural pressure determinations, it should be kept in mind that posture is an important modifying factor by

changing diaphragmatic position and excursions and the thoracic or hemithoracic girth and by altering the blood content of the lungs.

On induction of pneumothorax, three manometric observations must be interpreted:

1. *Oscillations:* The presence of oscillations indicates that the exploring needle is either in the pleural space, in the subparietal plane or in the lung. The oscillations are synchronous with respirations; their peaks coincide closely but not exactly with the extremes of the inspiratory-expiratory phases (Neergard and Wirz (36)).

2. *Absolute manometric reading:* The presence of subatmospheric (negative) pressure throughout the respiratory cycle indicates that the needle is in the pleural space; the presence of fluctuations around the zero point (barometric pressure) of the differential manometer indicates that the needle point is most likely in the lung (possible exception: extreme emphysema). Even with these general directions, doubt may arise in a given case as to whether the needle is in the pleural space or in the pulmonary parenchyma. Von Muralt (34) suggested a test that occasionally contributes to the solution of the question whether the needle point is in the lung or in the pleural space: the patient is asked to hold his breath with open glottis; if the intrapleural pressure remains the same during the apnoic phase, the needle is in the pleural space; if it moves towards atmospheric pressure, the needle is in the lung. But breath holding with open glottis is not easy for most patients.

3. *Amplitudes:* The amplitudes are a measure of the volume change of the pneumothorax space (in conformity with Boyle's law) and are herewith *an index of the discrepancy between the volume change of the hemithorax and the volume change of the respective lung* (see below).

Dynamics of the Pneumothorax Space

Normally the intrapleural pressure is less than atmospheric pressure. In the absence of pleural adhesions it is equal to atmospheric pressure minus the "retractive force" of the lung. It is to be noted that if the intrapleural pressure is expressed, as is commonly done, as the *difference* between it and the atmospheric pressure (for example, -5 cm. water) then the absolute amount of this figure is a measure of the pulmonary stress. Forces of cohesion and of surface tension between parietal and visceral pleurae are operative but quantitatively unimportant (v. Neergard (35)). The pressure in the normal pleural space oscillates approximately between -2 and -7 cm. of water with a mean static pressure of -5. The extremes which have been observed are according to Prinzmetal and Kountz (38) of the order of -50 to -60 cm. of water on maximal inspiration with the glottis closed (Mueller's experiment), and $+60$ cm. of water on maximal expiration with the glottis closed (Valsalva's experiment). In vital capacity measurements with the glottis open, a representative range of intrapleural pressures between inspiration and expiration is 25 cm. of water. During collapse therapy, normal values are rarely seen. Due to increase of elastic modulus of the lung (that is, increased stress for a given expansion) due

to fibrosis, parenchymal infiltration, bronchial stenosis, etc., the intrapleural pressure is usually considerably lower (more "negative").

When air at atmospheric pressure and temperature is introduced into the pleural space where the temperature is higher and the pressure lower, it expands and thereby acts as a force that moves, that is, performs work upon the enclosing structures. Indeed, the rise in temperature and decrease in pressure of the introduced air are a measure of the work done. The thoracic cage is moved out, the diaphragm is pushed down, the mediastinum is shifted toward the opposite side and the lung is reduced in volume. It is to be understood that the degree of each of these changes varies considerably with the amount of air injected, with the initial conditions in the pleural space, and with the elastic moduli of the structures involved (which vary from patient to patient and with the presence or absence of pathological processes). In general all must occur, each may or may not be practicably measurable, none are predictable as to extent, except within wide limits.

Upon creation of a pneumothorax, new static and dynamic equilibria are attained between the thoracic structures, the pneumothorax space, the lung and the atmosphere. The introduced air decreases in pressure as it expands and the elastic stress of the lung decreases as pulmonary tissue collapses. In a free pleural cavity, when the sum of these again equals atmospheric pressure, the further expansion of the pneumothorax space and collapse of the lung cease. But since the elastic stress of the lung is now less than before, the intrapleural pressure is greater. As a corollary, a rise in intrapleural pressure after insufflation indicates that some degree of pulmonary collapse has occurred, which, however, may be very small.

The amount of air injected, the degree of pulmonary collapse and the change in static intrapleural pressure are interrelated functions. In any particular instance, their relationships may be ascertained and quantitatively expressed. But they are in general different from patient to patient, and in the same patient at different times if a modifying pathological process be progressive. Hence they cannot be quantitatively generalized nor predicted.

The relationship between the amount of air injected and the degree of pulmonary collapse is, particularly for small free pneumothoraces, complicated by the concomitant change of hemithoracic volume. If a given amount of air distends the thorax relatively little, it compresses the lung relatively much and the intrapleural pressure rises appreciably. If, however, it distends the hemithorax relatively much the lung undergoes relatively little change of volume and the static intrapleural pressure rises only slightly. There are, however, definite physiological limits to the degree to which hemithoracic expansion can occur. Hence successive insufflations of air result in continued increase of pulmonary collapse and of static intrapleural pressure.

Pulmonary collapse is not quite synonymous with decrease in content of pulmonary air. Of the three factors involved, pulmonary tissue, air and blood, the last two are variables. Very little is known about quantitative changes in blood content in collapse, but it is indubitable that such occur (see Christie

p. 698). The reduction in pulmonary volume may occur by reduction in its content of air, of blood, or by some unpredictable degree of both. The reduction in pulmonary volume is the algebraic sum of the changes in content of air and blood.

Because pneumothorax results in change of hemithoracic volume (see Trocmé (51)) as well as change of pulmonary volume, and since pulmonary collapse is not necessarily synonymous with equivalent loss of air, in many instances less air is pushed out of the lung than is injected into the pleural space. This can be demonstrated in the following way:

If air is injected intrapleurally while spirometric tracings with a closed system are taken, it can be calculated from the graph how much air is removed from the lungs by the air injected into the pleural space (Christie (9)). In such experiments we obtained the following data:

PATIENT	PNEUMOTHORAX SIDE–EXTENT OF COLLAPSE	DURATION OF PNEUMOTHORAX	AMOUNT OF AIR INJECTED INTO PLEURAL SPACE	DECREASE OF AIR IN LUNG	AMOUNT OF AIR REMOVED FROM PLEURAL SPACE	INCREASE OF AIR IN LUNG
F. F.	L 90%	2 years	350 cc.	0	150 cc.	0
J. G.	L 60%	1 year	400 cc.	150 cc.	200 cc.	80 cc.
J. B.	L 20%	9 months	200 cc.	0	0	0
R. S.	L 60%	5 months	400 cc.	0	200 cc.	0

The statement in the table above that in 3 out of 4 patients the intrapleural injection of 200 to 400 cc. of air, and the subsequent withdrawal of 150 to 200 cc., did not produce a volume change of intrapulmonary air, must be understood as meaning "no change demonstrable by the method employed."

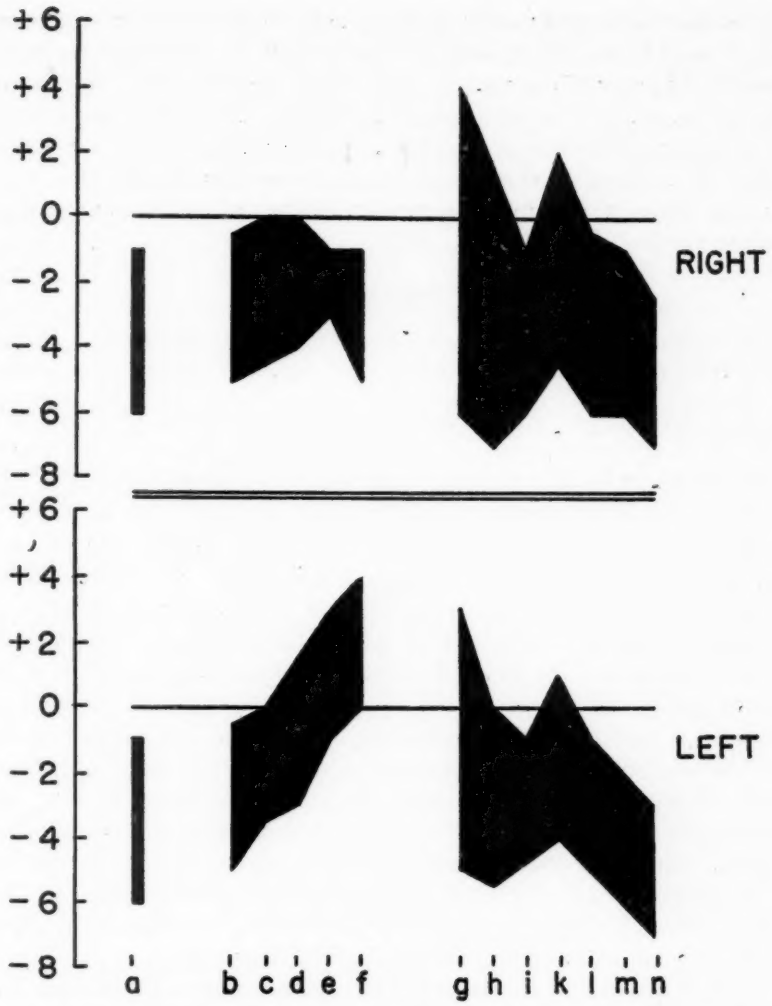
As a corollary to the preceding discussion, there is no simple relation between the amount of air injected and the change in static intrapleural pressure. This is a frequent clinical observation. The change in static intrapleural pressure is a covariant of the degree of pulmonary collapse produced (static interpleural pressure plus pulmonary stress equals barometric pressure) and, as shown above, this bears no constant relation from subject to subject to the amount of air injected. If the potential size of the pleural cavity is severely restricted (fibrosis of pleura, noncollapsible lung) little collapse of the lung can occur and the introduced air merely distends a small pocket and is compressed in it with concomitant relatively large rise in pressure. The situation is physically similar when the lung is completely collapsed and the pleural cavity has attained its maximal potential size. Conversely a large rise in static intrapleural pressure, following the introduction of relatively small amounts of air, indicates a relatively nonexpansile pleural cavity.

The relation between static intrapleural pressure and pulmonary volume is likewise pertinent. In a free pleural cavity, a high static intrapleural pressure indicates low pulmonary stress, while a low static intrapleural pressure means high pulmonary stress. With normal lungs, allowing for small individual differences, low pulmonary stress occurs with marked collapse and high stress with relative distention. In any instance the extent of distention is a function of

the particular elastic modulus. With diseased lungs, stress and expansion are not equivalent terms. In emphysema, for instance, a marked degree of expansion is associated with a low pulmonary stress (hence a high intrapleural pressure), while in fibrosis a high pulmonary stress (hence a low intrapleural pressure) is associated with a low degree of expansion. Since in many disease processes fibrosis and emphysema may coexist, the relation between static intrapleural pressure and degree of collapse or distention is unpredictable.

With respiratory movements, the gases in the pneumothorax space undergo practically isothermal compression and expansion. Therefore changes in pressure can be interpreted as changes in volume. The amplitudes of the dynamic intrapleural pressure, that is, the difference in intrapleural pressure between inspiration and expiration, are therefore a measure of the change in volume of the pneumothorax space with ventilatory movements. Small amplitudes mean small changes of pneumothorax volume, and large amplitudes mean large changes of pneumothorax volume. The quantitative computation is simple. The atmospheric pressure is usually close to 1,000 cm. of water. An amplitude of 5 cm. of water thus indicates a change in pneumothorax volume of approximately 0.5 per cent. All other things being equal, the amplitudes are first of all a function of the ventilatory movements of the thoracic cage (ribs and diaphragm). As these increase, the amplitudes increase, and vice versa. Secondly, with a given ventilatory movement of the thoracic cage, the change in volume of the pneumothorax space depends on the *discrepancy* between the hemithoracic change of volume and the concomitant change of pulmonary volume. If these two volume changes are almost equal and synchronous, the volume of the pneumothorax space is almost isometric and the intrapleural pressure almost invariant. If the amplitudes of the intrapleural pressure are large, the pneumothorax space is undergoing large changes in volume, indicating small changes in the volume of the collapsed lung. Finally, the amplitudes are a measure of the change in pulmonary stress between expiration and inspiration. Hence by making an approximate visual estimation of the degree of hemithoracic expansion, observation of the intrapleural pressure amplitudes serves as a rough measure of the change in volume of the pneumothorax space, of the change in stress upon the lung, of the relative degree of pulmonary movement and hence of the pulmonary distensibility. To recapitulate, small amplitudes mean either that the thoracic cage is moving little, and/or that the change in volume of the lung is closely following that of the thoracic cage, that is, the lung is moving freely under small stresses. Large amplitudes mean either large thoracic movements and/or loss of pulmonary distensibility (for example, parenchymal or pleural fibrosis, partial or complete blocking of bronchial tree or alveoli).

In some instance pneumothorax *per se* will lead to decreased hemithoracic movement, and hence will decrease intrapleural pressure amplitudes. Conversely, it might lead to increased amplitudes if pneumothorax induction abolishes pleural pain (for example, lobar pneumonia) that had caused thoracic splinting. For these reasons, the amplitudes of the intrapleural pressure are within wide limits independent of the amount of air injected and, indeed, bear no constant relation to it.



GRAPH 1. Intrapleural pressure amplitudes, left and right, in a rabbit during pneumothorax on the left. At a, 10 cc. of air was injected into both pleural cavities; between a and b one hour elapsed.

At b 20 cc. of air into left pleural space.
At c 20 cc. of air into left pleural space.
At d 20 cc. of air into left pleural space.
At e 20 cc. of air into left pleural space.
At f 20 cc. of air into left pleural space.
At h 20 cc. of air withdrawn from left pleural cavity.
At i 20 cc. of air withdrawn from left pleural cavity.
At k 20 cc. of air withdrawn from left pleural cavity.
At l 20 cc. of air withdrawn from left pleural cavity.
At m 20 cc. of air withdrawn from left pleural cavity.
At n 20 cc. of air withdrawn from left pleural cavity.

The relation between hemithoracic expansion and distention of the lung may be complicated by a shifting mediastinum or mediastinal herniation (see below).

Intrapleural pressure changes are measurably transmitted to the contralateral pleural space, unless the mediastinal structures are stiff (fibrous mediastinal pleuritis, a frequent occurrence in pneumothorax patients (Graham (22) Graham and Bell (21)). Graph 1 shows a pertinent observation in a rabbit.

Out of 3 patients with bilateral pneumothorax, a definite contralateral pressure effect was found only in one.

Pleural pressures

	Right	Left
Before refill on right	−7, +2	−12, −3
After refill, 300 cc	−7, +6	−12, 0

When pneumothorax is maintained over many months or years, secondary changes are likely to take place, notably a fibrous thickening of the pleura which is much enhanced by the frequent occurrences of pleural effusions. Furthermore, adhesions or obliterative pleurisy may develop. All of these decrease pulmonary mobility and distensibility, and the last reduces the volume of the pneumothorax space. In the presence of adhesions, the simple theoretic relation between intrapleural pressure, pulmonary stress and atmospheric pressure is profoundly altered. Adhesions act as a force operating in the same direction as the air pressure in the bronchial tree and oppose the intrapleural pressure. Moreover, adhesions are elastic bodies and their tension is a variable itself dependent upon the intrapleural pressure. At any moment of equilibrium, the sum of the stresses of all the adhesions plus the atmospheric pressure is equal to the sum of the intrapleural pressure and the pulmonary stress. Moreover adhesions and pleural fibrosis restrict the potential expansion of the pneumothorax space. Hence in the presence of adhesions, or of a relatively immobile lung due for example to pleural thickening, equal amounts of air refills produce a greater increase of intrapleural pressure than before, and with sustained thoracic movements, intrapleural pressure amplitudes become larger.

The thickening of the pleural surfaces causes a slower absorption of air and necessitates increasing the intervals between refills. For these same reasons, it is found quite regularly that a pneumothorax of short duration will be absorbed without producing excessively low intrapleural pressures, while during the period of pulmonary reëxpansion following prolonged pneumothorax treatment, the intrapleural pressure becomes quite low ("highly negative") (causing often so-called *ex vacuo* effusions) and the respiratory pressure amplitudes become quite large.

PNEUMOTHORAX GASES

Methods for the Study of Pneumothorax Gases

For the study of the behavior of pneumothorax gases it is necessary to know the volume of the pneumothorax space, the percentage composition of its component gases and the mean pressure so that the tensions of these gases may be calculated.

(*1*) The composition of the pneumothorax gases is determined by measuring the intrapleural pressure followed by the withdrawal of about 25 cc. of the gas and its analysis in duplicate by any suitable apparatus, such as the Haldane machine or its modifications. A needle in the pneumothorax space is connected through a three-way stop-cock with an evacuated gas sampling tube and with a manometer. The dead space between the needle and the sampling tube should be less than 2 cc. For the most rigorous work, a sampling tube modified so as to allow simultaneous determinations of pressure can be used. (See above under apparatus.)

(*2*) The method of determining pneumothorax volume commonly used is the determination of the quantitative changes occurring in the pneumothorax gases after dilution by a measured amount of gas of known composition. The technique of Matsuzawa (31) is as follows: Twenty-five cc. of pneumothorax air is removed for analysis. One hundred cc. of filtered room air of known composition, accurately measured in volume with a calibrated burette, is introduced into the pneumothorax cavity; 25 cc. samples are then removed for analysis at intervals of two and one-half to three and one-half minutes from the beginning of the administration of the test air. In the first week of pneumothorax, when diffusion of gases is rapid and the pneumothorax volume small, an additional sample may be taken at one and one-half minutes.

The calculations are as follows:

$$x = \frac{a(p - p_2) + b(p - p_1)}{p - p_2}$$

Here x is the pneumothorax volume to be determined.

a is the volume of pneumothorax air removed for analysis initially from x.

b is the amount of air added.

p the per cent volume concentration of some gas component in x.

p_1 is the percent volume concentration of this same gas in b.

p_2 is the percent volume concentration of this same gas in the pneumothorax air after the addition of b.

Carbon dioxide values are better suited than oxygen values for p, p_1 and p_2 in the calculation of the pneumothorax volumes.

The intrapleural pressure determinations are, for the sake of uniformity, always carried out with the patient in the same position and with the needle in the same location. The averages of the mean of several inspiratory and expiratory readings are taken. The absolute total pneumothorax air pressure is obtained from this value and the prevailing barometric reading. It is customary to express the results in terms of millimeters of mercury at 38°C.

Behavior of Pneumothorax Gases

Gas in the pleural space obeys the same laws that are operative in any closed space within the body, and it is well known that maintainance of such a space without replenishment is not possible. In all such spaces the gases approach equilibrium with the gases in the tissue fluids which in turn are in equilibrium with the gaseous tensions of the venous blood. The total gaseous tension of the venous blood is less than atmospheric pressure by about 50 to 60

mm. of mercury. As the system moves toward equilibrium, the total gas tension in the body space will approach that of the venous blood, namely about 700 to 710 mm. of mercury. But all tissues are directly or indirectly subject to atmospheric pressure. Hence the space will be diminished in size, the gases will undergo compression, their tensions will rise, their equilibrium with the venous blood will be disturbed and absorption will continue until complete (Rist and Strohl (39), Henderson and Henderson (23) and Coryllos and Birnbaum (12)).

The rate at which a mixed gas, such as air, is absorbed in the pleural space depends on the behavior of its constituent gases. The absorption or effusion of each depends on the usual well known factors—difference in gas tension between the two zones involved, the solubility and diffusion constants of the gas, the area of the diffusing surface and the thickness of the tissues through which diffusion must take place. The amount of diffusion is the product of the rate and time. There is no evidence that the pleura possesses any "gas secreting" properties and the entire process is apparently explainable by physico-chemical factors. Conditions in the pleural space and the properties of the gases are such that carbon dioxide and oxygen undergo rather rapid changes in tension, while nitrogen is absorbed much more slowly.

When gas is introduced into the pleura continuous readjustments follow, there being both progressive loss of volume (following a brief initial increase in volume caused by the warming of the gas) and changes in the relative composition of the pneumothorax gas. It has been found by serial studies (Matsuzawa (29, 30) Coryllos and Birnbaum (12)) that, although there is much variation between individual instances, there is a general characteristic pattern.

There must first be considered the behavior of a "dry" pneumothorax, that is, one which is not complicated by pleuritis or effusion. Under the usual conditions of induction and periodic refilling, there is initially a brief period of marked changes and subsequently a period of relative stability. Stability is to be understood as a relatively constant rate of change, rather than as an absence of change. Air is the most commonly used gas. Its oxygen content of approximately 20 volumes per cent shows a marked fall in the first twenty-four hours to the vicinity of 7 per cent, and then a gradual fall until about the fourth week when it attains a fairly constant level in the vicinity of 2 per cent (range 1 to 5 per cent). Carbon dioxide exhibits an immediate marked rise (by diffusion from the blood into the pleural sac) from its negligible values in atmospheric air and attains relative stability in about a week in the neighborhood of a concentration of 7 per cent (range 6 to 9 per cent). The nitrogen of the pneumothorax air thus comes to assume a value of about 90 per cent. After about a month, the gases show fairly stable daily absorption rates indefinitely, although there is often a tendency towards constant slight decrease in this rate, while the relative proportion of the gases remains fairly constant. *Representative* figures are for daily absorption rates: (*1*) In the period of induction: nitrogen 126 cc., oxygen 62 cc., carbon dioxide 11 cc., total daily absorption rate 199 cc. (*2*) After relative stability (one month): nitrogen 36 cc., oxygen 12 cc., carbon dioxide 1.5 cc., total 49.5 cc.

After each refill the proportions of the gases are usually restored within about twenty-four hours. Usually the amount of the refill is small compared to the size of the pneumothorax space. The change in nitrogen is slight, for atmospheric air contains about 79 per cent and the pneumothorax air about 90 per cent. The change in carbon dioxide will be the result of dilution, the amount in atmospheric air being so small, and is usually only significant if the pneumothorax volume is small or the refill large. The changes in oxygen will be greater, however, for the refill air has a concentration of about 20 per cent, while that of the pneumothorax air is usually in the vicinity of 2 per cent. For these reasons, in the initial period of pneumothorax, when the lung is undergoing relatively rapid decrease in volume and changes in the gas contents are rapid, frequent refills are required. But after some time, the pneumothorax space can be maintained at a relatively constant size by fairly uniform refills at regular intervals. Again by "constant" is meant a fairly uniform cycle of relatively small changes with approximately the same conditions reëstablished after each refill.

The fact that initially the absorption of gases is rapid, but subsequently decreases with the duration of the pneumothorax, focuses attention on changes in the absorbing surface, that is, the pleura. There is roentgenological and anatomical evidence of progressive pleural fibrosis. The circulation through the pleura is also a variable factor influenced by anatomical changes in the underlying diseased lung and its state of aeration. This is well brought out by the fact that pleuritis and effusion influence both the rate of diffusion of the gases and the quantitative composition of the pneumothorax gases. Although transient effusions cause but slight, transient or no effect, more extensive or longer lasting effusions or pleuritis cause a sudden marked decrease in the absorption rate of pneumothorax air, varying with the intensity of the process. The diffusion rate of carbon dioxide is but little changed, but the rates of absorption of oxygen and nitrogen are sharply decreased. As an example, a pneumothorax which showed a daily absorption rate of 100 cc. had an absorption rate of but 34 cc. after one month of a mild afebrile effusion, and this subsequently gradually decreased to about 15 cc. per day. This is in conformity with the clinical observation that with the onset of an effusion—and not infrequently a few days before it is fluoroscopically demonstrable—the refills must be suddenly decreased to maintain the previous intrapleural pressure. Simultaneously there is a change in the composition of the pneumothorax gases which now must also establish gaseous equilibrium with pathological fluids. This is in the direction of a further drop in oxygen values and a further increase in carbon dioxide content. As an example, the oxygen usually falls below 0.25 per cent and the carbon dioxide rises to 9 to 14 per cent, figures rarely seen in the absence of pleuritis or effusion. There is some relation between the pH of the exudate and the carbon dioxide of the pneumothorax air, a falling pH being associated with a rising carbon dioxide content.[4]

[4] The specific examples quoted in the above discussion are from Matsuzawa (loc. cit.).

Physical Methods in the Diagnosis of Bronchopleural Fistulae

A diagnosis of bronchopleural fistula may be made by any of the following procedures, the highest percentage of diagnoses being made when all three are carried out.

1: Pressure test: Air is withdrawn from the pneumothorax space, and the intrapleural pressure falls. If this decreased pressure is not sustained, then air is leaking into the pleural space. If it is certain that such leaks are not occurring in the apparatus, then a bronchopleural fistula is present. The test is simple and good if the connections of the apparatus are indubitably air-tight.

2: Methylene blue is introduced into the pleural space. If it appears in the sputum, there is a bronchopleural fistula. This test is best carried out in the presence of an effusion, which however is usually present in bronchopleural connections. A negative test is inconclusive.

3: Gas analysis: (See above for technique) (Matsuzawa (32) Coryllos and Birnbaum (12)).

A bronchopleural fistula is probably present:

a. If the carbon dioxide value is less than 5 per cent and the oxygen value is more than 7 per cent.

b. Since in pleural effusions, the carbon dioxide is usually above 9 per cent, if values above this figure are obtained, a concomitant value of more than 1 per cent oxygen is indicative of a fistula, for in effusions the oxygen value is usually below 0.25 per cent.

If the bronchopleural connection is wide open, the above rules have a high presumptive value. However, their absence does not rule out bronchopleural fistula, for such may be open only intermittently. To increase the percentage of diagnoses, then tests *1* and *3* may be combined. Air is withdrawn to decrease the intrapleural pressure (at least to -25 cm. of water) in the hope of temporarily forcing the bronchopleural fistula to leak. Theoretically a dilution of about 2 per cent of the pneumothorax air by alveolar air is detectable. The gas is now withdrawn for analysis and the above rules applied. The reliability of the gas-analytical method can be increased by having the patient breath oxygen for one-half to one hour before the gas sample is removed from the pleural space (G. C. Leiner in unpublished observations).

EFFECT OF PNEUMOTHORAX ON THE LUNG

Bronchospirometry

Until the introduction of the bronchospirometric method, the effects of pneumothorax on ventilation was limited to spirometric studies.

It is obvious that a number of observations that are valid for normal or symmetrically diseased lungs (emphysema, silicosis) are not applicable to the condition of unilateral collapse therapy. Two examples are offered:

(*1*) The ventilation equivalent (Anthony (4)), that is, the amount of air that must be ventilated in order that 100 cc. of oxygen be absorbed, is a numerical expression of ventilatory efficiency in terms of respiration (that is, in further analysis of the efficiency of pulmonary circulation). It was disappointing to

find that the ventilation equivalent as determined by spirometry, contrary to sound theoretical expectation, bore no obvious relation to the functional damage of lungs (Anthony (4), Moncrieff (33)). When the ventilation equivalent is determined by bronchospirometry for each lung separately, its significance becomes apparent. Table 1 lists the total ventilation equivalents in comparison with those of single lungs in cases of different degrees of pathological involvement and with collapse measures. This table clearly shows how a well functioning contralateral lung obscures the significance of the ventilation equivalent in predominantly unilateral involvement.

(*2*) Christie and McIntosh (8) have established a valuable method for measuring the elastic forces of the lung by measuring simultaneously intrapleural pressure amplitudes and tidal air. The pressure amplitudes represent the force

TABLE 1

Comparison of ventilation equivalent as determined by spirometry and by bronchospirometry. The former value is within the normal range in all examples shown. (Data from Montefiore Hospital, Division of Pulmonary Diseases, New York City)

PATIENT NUMBER	SPIROMETRY, TOTAL	BRONCHOSPIROMETRY	
		Left lung	Right lung
62	2.9	4.6	2.1
50	2.4	1.2	4.7
151	3.1	5.1	1.8
69	2.8	5.7	2.7
51	2.6	6.3	2.2
171	2.9	1.8	6.3
49	2.7	6.3	2.3
56	2.2	7.4	2.6
74	2.8	2.1	8.2
46	2.2	10.3	2.3
69	1.9	16.4	2.2

and the tidal air the work done; the relation between the two is the pulmonary distensibility.[5] In asymmetrical involvement or during collapse therapy the method is not applicable, since spirometry does not permit measurement of the tidal air of each lung separately (which in one lung is often a multiple of that in the other lung) and since the pleural pressure amplitudes differ greatly in the two sides. Therefore, pulmonary elasticity could be measured only by determining bronchospirometrically the tidal air separately for each lung and by recording the intrapleural pressure bilaterally. This requires a set-up that would be formidable to the patient. Using the original spirometric method, it is found that the pulmonary distensibility decreases with each pneumothorax refill; but such measurements indicate, at best, directions and not quantities.

[5] Christie and McIntosh (8) have defined the unit of pulmonary distensibility as the force in cm. H_2O which must be applied to the surface of the lung to yield an increase in lung volume of 100 cc. Only bronchospirometric measurements can establish such a volume increase for each lung separately.

From a practical point of view the functions of bronchospirometry are:

(*1*) To determine the relative function of left and right lung. Clinical and roentgenological criteria are often misleading, particularly since undiagnosable pleural obliteration frequently reduces function more than easily diagnosed parenchymal disease (Pinner, Leiner and Zavod (27, 37)). It must be emphasized that the total function must be determined by spirometry, since bronchospirometry, because of a ventilatory stenosis and non-basal condition of the patient, leads to unpredictable alterations.

(*2*) To determine the functional loss produced by different collapse therapy measures. Spirometry alone yields incomplete data because it does not permit one to account for compensatory processes in the contralateral lung. (For more detail and literature regarding bronchospirometry, see Pinner, Leiner and Zavod (37)).

Pulmonary Volumina

Vital capacity: The vital capacity may decrease following the introduction of air into the pleural cavity, but this decrease is less in amount than the amount of air injected and bears no direct nor simple relation to it. (Anthony and Heine (3), Bendove (6), Herms and Rüttgers (24) and many others.) As shown above, following the establishment of pneumothorax, thoracic volume changes continue to be reflected in volume changes of the lung, since the pneumothorax air itself undergoes but slight changes in volume (2 to 3 per cent) on maximum ventilation. The collapse that occurs in the lung is largely at the expense of the residual air and this does not contribute to vital capacity measurements (Anthony (4) and Cournand and Richards (16)). In longer standing pneumothoraces, there is often considerable decrease in vital capacity, but this is the result either of pneumothoraces so large that the lung is completely collapsed before the act of expiration is completed or of relative immobility of the hemithorax, diaphragm or lung due to pathological changes. In addition:

(*a*) Diseased portions of lung, containing air that is not moved with ventilation, are collapsed; hence the collapse of such areas does not affect the vital capacity.

(*b*) In chronic pneumothorax, both hypertrophy of ipsolateral respiratory muscles and contralateral pulmonary compensation may occur (Addis (1), Hilber (25)).

Examples of the effect of pneumothorax refills on vital capacity

PATIENT	VITAL CAPACITY		CHANGE IN VITAL CAPACITY	AMOUNT OF AIR INJECTED
	Before refill	After refill		
	cc.	*cc.*	*cc.*	*cc.*
N	2,350	2,250	−100	200
C	3,650	3,650	0	250
K	2,800	2,725	−75	200
P	1,725	1,675	−50	200
O	1,800	1,800	0	200

These determinations were made immediately before and after refills; each vital capacity is the mean of three determinations.

Subdivisions of pulmonary volume: Changes in other pulmonary volumina are best shown in the graphs below. These graphs must be understood as individual and representative examples, but not as a means or rules: Individual variations due to different forms of disease are too numerous to allow generalizations.

Graph 2 refers to a patient whose spirometric and bronchospirometric studies were done immediately before induction of pneumothorax on the left side and again five months following induction at which time her left lung appeared about 60 to 70 per cent collapsed. Before induction, her total vital capacity was about 3,000 cc.; about 50 per cent of this was complementary air (about normal), about 20 per cent tidal air (somewhat above normal) and 30 per cent was reserve air (somewhat reduced). Following collapse, her reserve air was cut to less than one-third; that is, her lung was closer to expiratory position; her tidal air was but little reduced and her complementary air showed a marked reduction, but less than the reserve air. The second column, showing the pulmonary volumina in terms of percentages, shows clearly that the reserve air is the only subdivision that was reduced in percentage.

The bronchospirometric data concerning the left lung show the same condition in exaggerated fashion, while the right lung does not show any percentage deviation from the preoperative level; its vital capacity is somewhat reduced due to a shift of the mediastinal structures to the right.

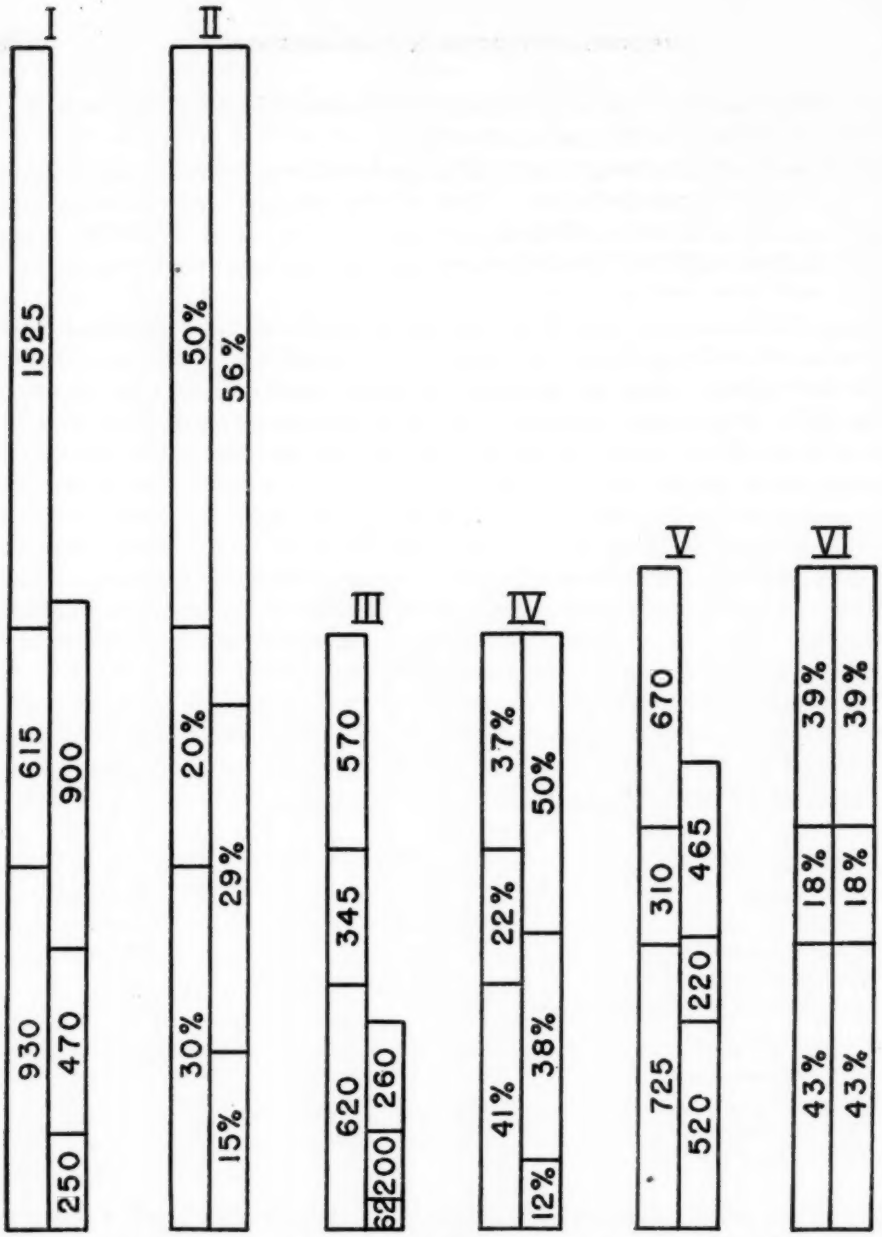
Additional Data

Spirometry	Before	After[6]
O_2-intake	267 cc.	219 cc.
Minute volume	6,750 cc.	5,650 cc.
Ventilation equivalent	2.2	2.2
Maximum breathing capacity	83,400 cc.	45,000 cc.

	Right		Left	
Bronchospirometry	Before	After	Before	After
O_2-intake	159 cc.	162 cc.	148 cc.	88 cc.
Minute volume	5,870 cc.	4,830 cc.	6,510 cc.	4,360 cc.
Ventilation equivalent	3.1	2.6	3.8	4.3

Graph 3 presents a patient before and two and one-half months following induction of pneumothorax on the right; collapse was only about 30 per cent. Here, too, is shown the shift towards the expiratory position with marked reduction of reserve air. Following pneumothorax, the tidal air is an almost three times greater percentage of the total vital capacity—a measure of compensation that entails a reduction of respiratory reserve. The collapsed right

[6] At the time of the second examination the patient's former febrile temperature had become practically normal.



GRAPHS 2 and 3. Spirometric and bronchospirometric determinations of pulmonary volumina before and after collapse therapy. Each double column represents precollapse figures in the first half column, postcollapse figures in the second half column.

Column I: Spirometric data, absolute figures.

Column II: Spirometric data, percentage figures.

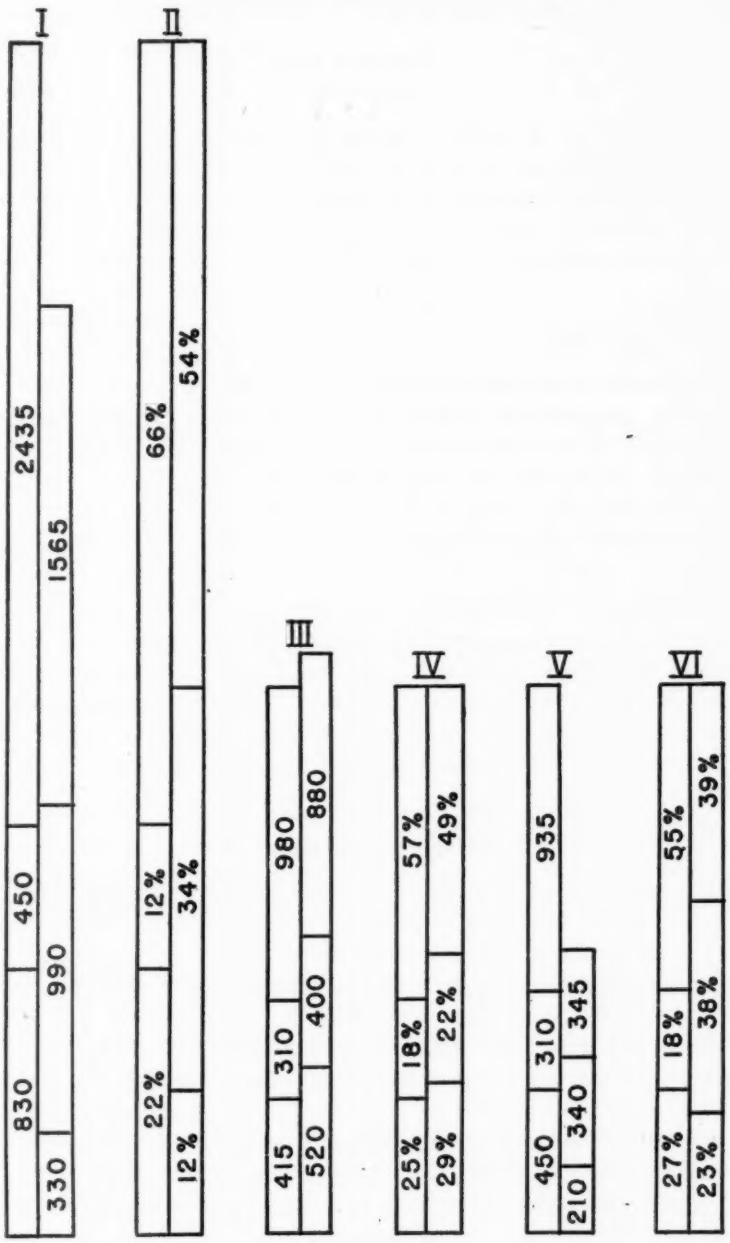
Column III: Bronchospirometric data: left lung, absolute figures.

Column IV: Bronchospirometric data: left lung, percentage figures.

Column V: Bronchospirometric data: right lung, absolute figures.

Column VI: Bronchospirometric data: right lung, percentage figures.

In each column the uppermost division represents complementary air; the middle division, tidal air and the lowest division, reserve air.


I
2435
450
830
1565
990
330
II
66%
54%
12%
34%
22%
12%
III
980
880
310
400
415
520
IV
57%
49%
18%
22%
25%
29%
V
935
310
345
450
210
340
VI
55%
39%
18%
38%
27%
23%

GRAPH 3

lung alone is affected, while the contralateral lung shows practically no change. Here, there was no mediastinal shift.

Additional Data

Spirometry	Before	After
O_2-intake	222 cc.	217 cc.
Minute volume	5,380 cc.	6,900 cc.
Ventilation equivalent	2.1	2.7
Maximum breathing capacity	54,900 cc.	56,500 cc.

Bronchospirometry	Right		Left	
	Before	After	Before	After
O_2-intake	88 cc.	150 cc.	212 cc.	187 cc.
Minute volume	4,940 cc.	5,100 cc.	4,940 cc.	6,040 cc.
Ventilation equivalent	4.8	2.9	2.0	2.8

Spirometric and bronchospirometric determinations of pulmonary volumina are subject to considerable unavoidable deviations, even in the same individual. Christie (7) has published some pertinent data on this subject.

Residual air: During the last two decades, the estimation of residual air has undergone important technical improvements (Darling *et al.* (17)). One should, therefore, treat with scepticism many figures published for residual air in various pulmonary conditions. The latest and probably most reliable figures concerning residual air in collapse therapy are those of Darling *et al.* In general, it can be said that pulmonary collapse decreases residual air. This is a most important phenomenon, because it explains why a considerable relaxation of lung tissue is possible without a proportional decrease of ventilatory function.

For other spirometric data in connection with pneumothorax treatment see Anthony and Heine (2, 3), Cousnand and Richards (16), Schmidt and Gaubatz (41), Anthony (4, 45).

Pulmonary Parenchyma

Air in the pleural space reduces the volume of the ipsilateral lung as shown in the graphs above and thereby reduces the elastic stress of the lung tissue. (This is probably one important therapeutic factor.) As mentioned above, pleural and parenchymal fibrosis which usually progress during collapse treatment decrease the pulmonary distensibility. Christie (9) has shown that pneumothorax refills *per se* in the acute experiment have the same effect; this necessitates the conclusion that collapse increases (acutely!) the blood content of the lung.

With a pneumothorax of subatmospheric pressure (as commonly practised now) the retraction of pulmonary tissue is fairly uniform throughout a normal lung. Pneumothorax frees the lung from the inner contours of the pleural space and permits it to assume the shape dictated by its own immanent elastic moduli (51). Disease (infiltration, fibrosis) produces areas in the lung whose elastic moduli differ (usually greater) from the surrounding relatively normal areas (Van Allen and Wu (43)). Hence these areas under a given inflationary stress are less expanded than the normal tissues, resulting in an unequal collapse

termed "selective collapse." The same effect is produced in portions of the lungs that on account of bronchial stenosis or occlusion are less well or not at all aerated.

MEDIASTINUM

Reference has been made repeatedly to the shifting of the mediastinal structures during collapse therapy. If these structures are flexible they will, of course, deviate towards the side of lower pressure, that is, towards the non-collapsed side. The mediastinal shift is more prominent in expiration than in inspiration, indicating that the pressure difference between the two pleural cavities is greatest in expiration.

The same considerations apply to the more infrequent phenomenon of mediastinal herniation which occurs usually in either one or two "weak" portions of the mediastinum, namely, in the upper anterior or in the lower posterior portion. Herniation, like shifting, is most clearly visualized in expiration. The content of the hernia is either pneumothorax gas (at times pleural effusion) or lung. In late phases of pneumothorax, particularly during reëxpansion with very low intrapleural pressures in the pneumothorax, the non-collapsed and, at times, emphysematous contralateral lung may herniate into the pneumothorax side (Barnwell (46)).

Fenestration of the mediastinum is extremely rare in man, (Smith and Willis (42)), frequent in dogs (Ebina (19)), constant in guinea pigs. This information is important—and has sometimes been overlooked—for the selection of proper experimental animals.

PHYSICAL FACTORS PROMOTING HEALING IN COLLAPSE THERAPY

It is not within the scope of this paper to discuss all the many factors that may contribute to the beneficial effect of collapse therapy. There is no unanimity in the literature on this subject, and most factors that are held responsible are not of a strictly physical nature. The strictly physical factors are:

1: Decrease of elastic tension.
2: Decrease or cessation of ventilatory movements of the diseased portions of the lung.

The mechanism of these factors has been discussed above. Cessation of ventilatory movement is caused in some cases by a mechanism that has not been mentioned before, namely, atelectasis produced by bronchial occlusion (Coryllos (13)). The development of atelectasis may in some patients be enhanced by collapse therapy, mainly by kinking of bronchi, particularly if bronchial stenosis preëxisted. Following bronchial occlusion—in the absence of virulent pyogenic infection—the intraälveolar gases are resorbed by the bloodstream and the parenchyma becomes airless, that is, atelectatic. Tuberculous foci in atelectatic lung tissue show a definite tendency to fibrotic encapsulation and healing. The same process may cause the collapse and subsequent healing of tuberculous cavities.

Other factors that are deemed important in the beneficial effect of collapse therapy will only be listed:

1: The slowing of the air stream in shortened and dilated bronchi in addition to a decrease in total ventilation helps apparently to prevent intrabronchial dissemination of tubercle bacilli.
2: In marked collapse, the circulation in the lung tissue is decreased, minimizing the danger of haematogenous dissemination.
3: Decreased lymph flow diminishes the transport of toxic products from tuberculous foci with abatement of toxaemic symptoms.
4: Relative anaemia and lymph-stasis may enhance fibrosis.

SUMMARY

Adequate discussion of the physical factors concerned in pneumothorax treatment are singularly lacking in the literature.

This paper presents an attempt of providing a concise exposé of the interrelation of the main physical factors operative in pneumothorax.

The discussion is concerned with the following points:

1: The elastic properties of the lung.
2: Methods used in the study of ventilation, such as spirometry, bronchospirometry, pneumothorax machines, manometry and techniques for the study of intrapleural gases.
3: Physical factors concerned in intrapleural pressure.
4: Dynamics of the pneumothorax space.
5: The behavior of pneumothorax gases.
6: Physical effects of pneumothorax on the lung, particularly its effects on pulmonary volumina, as determined by spirometry and bronchospirometry; and the effect on the pulmonary parenchyma.
7: The rôle of the mediastinum in pneumothorax.

SUMARIO

En la literatura brilla por su ausencia toda discusión adecuada de los factores físicos que intervienen en el neumotórax terapéutico.

Este trabajo trata de ofrecer una exposición concisa de la interrelación de los principales factores físicos que intervienen en el neumotórax, discutiendo los siguientes puntos:

1: Elasticidad del pulmón.
2: Métodos utilizados para el estudio de la aireación, tales como espirometría, broncoespirometría, aparatos de neumotórax, manometría y técnicas para el estudio de los gases intrapleurales.
3: Factores físicos que intervienen la presión intrapleural.
4: Dinámica del espacio del neumotórax.
5: Comportamiento de los gases del neumotórax.
6: Efectos físicos del neumotórax sobre el pulmón, en particular sobre los volúmenes pulmonares determinados por la espirometría y la broncoespirometría; y efectos sobre el parénquima pulmonar.
7: Papel del mediastino en el neumotórax.

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OSTEOPLASTIC THORACOPLASTY[1]

LEO ELOESSER

My old friend, Allen Krause, would scarcely have objected to printing in the AMERICAN REVIEW OF TUBERCULOSIS an article concerned primarily with surgical technique, but the sketchy presentation and the omission of fundamental anatomical studies would, I fear, have displeased him. The war and occupations connected with it may explain, if they cannot excuse, the reason for this short descriptive communication and the reason for foregoing necessary anatomical studies, which must be deferred to more leisurely times, or left to the work of others.

Clinical and pathological study of cavity formation and cavity closure has shed some light on the formation of cavities and the rôle of intracavitary pressure, but has failed to clarify greatly the processes underlying their cure; whether the usual process of healing is that of obliteration of the communicating bronchus and inspissation, perhaps even absorption of the cavity contents, or that of a concentric shrinkage, or a synechial fibrosis and adherence of the cavity wall, is not clear; neither has the rôle of collapse (that is, the release of the surface of the lung from negative pressure), compression or deflation in cavity treatment been explained. The first two methods, collapse and compression, at least, have two inherent elements, inseparable accompaniments of each other, each of which may cause a cavity to disappear, namely, immobility and atelectasis. Immobility, arrest of respiratory inflation and deflation, whatever its causes may be, external or internal, leads to atelectasis. Whether atelectatic exclusion of oxygen suffices to make the tubercle bacillus nonviable, or whether it is immobility which simultaneously causes the contained air to be absorbed from a cavity and the surrounding tuberculosis to heal, is not certain, despite much work on the part of Coryllos and others.

Reviewing old films, considering the pulmonary apex as it appeared when exposed at operation, considering the many unsatisfactory attempts at closing large apical cavities, an operation was determined upon about a year ago, which, it was thought, might immobilize the pulmonary apex more efficiently than previous thoracoplastic methods had done and more selectively, leaving the chest wall over the unaffected areas of lung comparatively intact. The scheme was evolved during the course of an extensive thoracoplasty for a large tuberculous empyema, when it was found that approximating the anterior ends of the *lower* resected ribs to the spine accomplished little or no reduction of the empyema space, but that wiring of the anterior ends of the second and third ribs to the lower posterior rib stumps, or their transverse processes, diminished the size of cavity surprisingly.

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Relation of one case history will suffice:

M. C., a patient kindly referred by Dr. Philip Pierson had a cavity in his upper right chest, probably tuberculous in origin. Besides the cavity he had a diffuse miner's disease of the lung. Attempted pneumothorax had proved unsuccessful in collapsing the cavity. Thoracoscopy had revealed adhesions in the posterior portion of the chest which were thought to be too broad to cut safely. The pneumothorax having proved inefficacious, it was allowed to recede. It was thought at the time of operation that it had been completely absorbed. It was also thought that it was unlikely that the cavity at the right top would close; furthermore, that this cavity represented, if not the sole, probably the major source of the man's bacilliferous sputum.

It was determined to attempt its closure by thoracoplasty. This procedure seemed justifiable in spite of the man's fifty-four years and the diffuseness of his disease because of the evident futility of more conservative methods.

Operation: (March 3, 1941). Accordingly, an angular incision was made over the right chest and scapula, exposing the upper three ribs, as usual. Upon freeing the periosteum it was thought, when novocainizing the ribs, that free pneumothorax still existed. Upon removing the periosteum from the third rib with the cautery the pleura proved to be unexpectedly thin and the pleural cavity was immediately entered. A section of the third rib about two inches in length was removed and the pleura still further opened, utilizing this posterior opening for exploration. There were some fine adhesions holding the apex of the lung to the pleura, these adhesions having formed blackish strands that might easily have been cut. They did not look like the adhesions thought to have been seen through the thoracoscope. However, upon Doctor Pierson's calling attention to the fact that these adhesions apparently lay higher than the ones which were seen, the hand introduced downwards encountered a broad area about twice the size of a dollar over which the lung was adherent to the posterior portion of the pleura. This overlay the area of the fourth and fifth intercostal spaces. Deliberating what might be done to close a cavity at this level without an undue amount of rib resection, the pleura in the region of these adhesions was loosened in the plane of the endothoracic fascia as in an ordinary extrapleural pneumothorax. It was easy to secure this free space by blunt dissection with the finger. Once obtained, however, means of preventing reëxpansion of the pleura were sought. About two inches of the fourth and fifth ribs were then resected, and after some difficulty the free anterior ends of the second and third ribs were surrounded with a clove hitch of steel wire, and this hitch in turn was passed around the posterior portion of the thoracic cage at a lower level in this manner; namely, the wire around the second rib was passed through a drill hole made through the stump of the resected fifth rib and its corresponding transverse process, thus pulling the second rib down to the level of the fifth. The wire around the third rib was passed through the sixth intercostal space and around the unresected sixth rib, thus approximating the anterior end of the third rib to the posterior portion of the sixth one. This manoeuvre really reduced the diameter of the upper portion of the chest (probably by securing a strong downward pull) even more effectively than is done by a subtotal Sauerbruch thoracoplasty. Before introducing these wire sutures a pull in the opposite direction was tried by approximating the ends of the previously resected fifth rib. The narrowing of the chest in the diameter which lifted up the lower front part toward the upper back part was nowhere comparable in efficacy to that secured by pulling the anterior portion of the upper ribs downwards and posteriorly as described above. In order further to facilitate this reduction in volume of the chest before definitely placing the wire sutures,

the first rib was resected, practically all of it being removed. The upper three ribs were resected with a Percy cautery; on the lower ones in order to further their subperiosteal regeneration a raspatory was used. The chest was closed without drainage. The man was moderately dyspnoeic for a few days. He was discharged to his home in a few weeks but reëntered ten months later and died of progressive pulmonary and intestinal disease.

The technique of operation may be adjusted to the size and position of the cavity and to a single stage or multiple thoracoplasty. Local infiltration anaesthesia is reinforced with enough sodium pentothal given intravenously to keep the patient lightly asleep. An angular incision is made with a vertical limb reaching from the top of the second rib to the fourth intercostal space and a horizontal limb inclining laterally and downward for about three inches. The trapezius and rhomboid fibres are separated with scissors, the index finger or the thumb is inserted into the opening, the muscles picked up between the thumb and forefinger and incised close to the spine with a scissors. If the incision is made far enough medially to avoid the descending branch of the transverse cervical artery, bleeding is nil. The intercostal spaces are then infiltrated with novocain, anaesthetizing the intercostals and pushing away the pleura. The posterior portion of the third rib is freed of periosteum with the galvanocautery, the rib is cut across at the transverse process. The rib is picked up with a lion-jaw forceps and its periosteum destroyed with the cautery or taken with the rib by severing the intercostal attachments with a scissors. An appropriate amount of the rib, usually about three and a half to four inches, is removed. If a low apical cavity makes it seem likely that the anterior portion of the third rib may be useful later, the resection may be more sparing. The second rib is then freed; its posterior periosteum is also destroyed with the cautery, its anterior part is mobilized by incising the intercostal attachments with a scissors. Raspatories and periosteal elevators are not used, so that there may be no irregular plaques of bone formed by the separated periosteum. The rib is transected at the transverse process, but is not resected anteriorly. The apex is pushed away from the first rib and the rib freed from underneath with the cautery, transected at its transverse process and pulled strongly downwards with a lion-jaw forceps. The scalenus attachments are freed with a scissors and the entire rib removed. The apex is inspected and palpated; if it seems desirable to displace it downwards, this is accomplished easily by infiltrating the endothoracic space with 0.25 per cent procain. The resulting oedema loosens the apex almost automatically.

From this point on several courses are open to the operator. If the cavity lies above the level of the fourth intercostal space and it seems as though a single stage of rib resection might accomplish its collapse, a hole may be pierced into the posterior end of the second rib by grasping it between the branches of a towel clip. A piece of triply braided #24 gauge, stainless steel wire, threaded on a strong, curved, cutting edge needle (a Martin needle), is passed through this drill hole, looped around the rib anterior to the drill hole and passed under the first half-loop in the form of a clove hitch. This is necessary in order that

the wire may not tear out of the drill hole or slip off the end of the rib, for its pull is very considerable. The free end of the wire is then passed, by means of the needle, through the fourth intercostal space, as close to the spine as possible, and out over the fourth rib. Care is taken not to include the intercostal nerve in the wire. By tightening the two ends of the wire the anterior stump of the second rib is drawn back to the fourth transverse process and the area occupied by the displaced pulmonary apex obliterated, or the apex itself firmly compressed. The procedure has been varied recently. It seemed as though obliteration of the dome of the chest would be still more thorough were the second rib rotated 180°, so that its convexity, instead of curving outwards, curved inwards. This was done by nicking the lower portion of the second costochondral junction with the rib shears and then twisting the rib 180°. This so loosened it that it was an easy matter to push the end of the anterior stump through the fourth intercostal space and to fasten it with a wire looped around the fourth rib, as one might push a stick between the palings of a picket fence and fasten it in place. The periosteum was scraped off the fourth and the second ribs at the points at which they crossed, in the hope that they might unite with bony union. This manoeuvre made a firm, bony roof over the depressed apex and so diminished the size of the upper thorax that the inward drop of the scapula was quite striking.

Should the first stage prove insufficient and the cavity persist, a second stage is undertaken. The interval between the first and second stage is immaterial, for the use of the cautery and scissors as recommended above efficiently and permanently obviates an outgrowth of new bone. The scar is excised. A vertical downward limb is added to expose the fourth, fifth, and sixth ribs, and an appropriate amount of as many of these ribs as may seem necessary is resected. Laterally, where the ribs are not covered by scapula, resection is done subperiosteally with the aid of a raspatory, for an aperiosteal resection leaves the unprotected front and side of the chest extremely loose and unstable; posteriorly resection of ribs up to the seventh is done aperiosteally by cauterization. The ends of the second and third ribs are freed from the scar to which they have become attached; the wire is unlooped from around the fourth rib and after resection the free end of the second rib is drawn as tightly as possible to the seventh transverse process. It may not quite reach. It may leave a gap of an inch or so to be bridged over by the braided stainless steel wire. The free end of the third rib may be encircled and a further collapse obtained by pulling it down and back to the seventh transverse process. The loops which encircle the second and third ribs may be twisted together, so that they form a Y, with its stem on the seventh transverse process and the fork on the second and third rib ends. Many variations will suggest themselves that may adapt each particular thoracoplasty to the site and size of the cavity it is intended to obliterate. The operation has the advantage of being peculiarly variable and of obliterating fairly exactly and selectively that portion of the thorax which it is proposed to collapse.

It has been a little difficult to nick the anterior costochondral junction of

TABLE 1

List of osteoplastic thoracoplasties done up to March 3, 1942

NAME	DATE OF OPERATION	RIBS RESECTED	RIBS WIRED Rib = C Intercostal space = ICSp	POST OPERATIVE RESULTS Cavity closed	 Sputum	REMARKS
M. V.	2- 5-42	1-3	C_2 rotated and pushed through $ICSp_4$	Yes		
M. C.	3-13-41	1-5	C_2 to 5th transverse process; C_3 to $ICSp_5$	No	Positive	Wire broke. Died February, 1942, progression of disease. Tuberculous silicosis (First case)
Mr. O.	3-10-41	1-3	None	No		
	7- 2-41	4-6	C_3 to C_6	Yes	Negative	
Mrs. S.	Sept. 1941	1-3	None	No		
	10-13-41	4-7	C_2 to C_8	Yes	Negative	
A. M.	12- 1-41	1-4	C_3 rotated and pushed through $ICSp_5$	No	Positive	
R. B.	10-31-38	1-3	None	No		Suction drainage May, 1940
	7-29-40	4-7	None			
	5-26-41		C_2 to 4th transverse process	Yes	3 cc. +	
L. S.	5-26-41	1-3	None	No	Negative	
	7-21-41	4-5	C_3 to C_6	Yes	Negative	
G. W.	12- 1-41	2-4	C_3 to C_5	No		
	2-16-42	1-5	C_2 and C_3 to C_6	?	?	
I. D.	6- 5-41	1-3	C_2 to C_4 (wire broke)	No	Positive	
	7-24-41	4-6	C_2 to C_7	Yes	Negative	
M. K.	7-26-41	1-3	None	No	Negative	
	10- 6-41	4-6	C_2 to C_7	Yes	Negative	
R. C.	6- 7-41	1-3	None			
	8-14-41	4-7	C_2 to $ICSp_6$			
	2-15-42	8-10	None	No	Positive	
L. T.	1-22-42	1-3	None			
	2-14-42	4-6	C_2 to C_7	?	Positive	
R. J.	2- 7-42	1-3	C_2 to C_4	No	Positive	
	3- 3-42	4-5	C_2 to C_6	?	?	
D. P.	2- 9-42	1-3	C_2 to C_4	?	Positive	

the second rib through the small posterior incision when the rib was to be rotated 180°. It may be better to do this part of the operation through a small anterior opening.

Postoperative convalescence has been uncomplicated and scarcely different to that of the ordinary thoracoplasty. Oxygen inhalation, transfusion and other measures which may indicate that the surgeon has overstepped the bounds of an operation which should for the most part be innocuous have not been found necessary.

The wire itself, as might be expected, has provoked not the slightest reaction. When exposed at a second stage operation it was found imbedded in a firm, reactionless scar with no signs of corrosion. At first when a single strand was used the wire broke, apparently very soon, in the first few days after operation; the use of heavier wire did not prevent breakage, which was thought to be due to the constant small movements to which respiration subjected it. A loose braid of three strands of #24 wire has proved more resistant, but even this has broken at times.

A similar but more extensive osteoplastic operation has been used in 3 cases of tuberculous empyema in which far reaching reduction of the rib cage was indicated.

SUMMARY

An osteoplastic thoracoplasty is described which collapses a portion of the chest efficiently and selectively by wiring one or more of the anterior stumps of the upper resected ribs to one or more vertebral transverse processes, or to the posterior portion of various lower ribs. A procedure is described which still further diminishes the size of the chest by rotating an upper rib 180° (so that its convexity looks inwards) and pushing its free end through the medial corner of one of the lower intercostal spaces. One case history is related and 14 are cited.

SUMARIO

Se describe una toracoplastia osteoplástica por la cual se efectúa el colapso eficaz y selectivo de una parte del tórax, amarrando con alambre incorrosible uno o más de los muñones de las costillas superiores a uno o más de las apófisis vertebrales transversas, o bien a la parte posterior de varias de las costillas inferiores. Se describe otra forma del mismo procedimiento por la cual se mengua aun más el volumen torácico, dando media vuelta a un muñón superior (de manera que la convexidad quede hacia adentro en lugar de afuera) e introduciendo el libre del muñón por el angulo mediano de un espacio intercostal inferior.

Se relata la historia de un enfermo y se citan catorce casos.

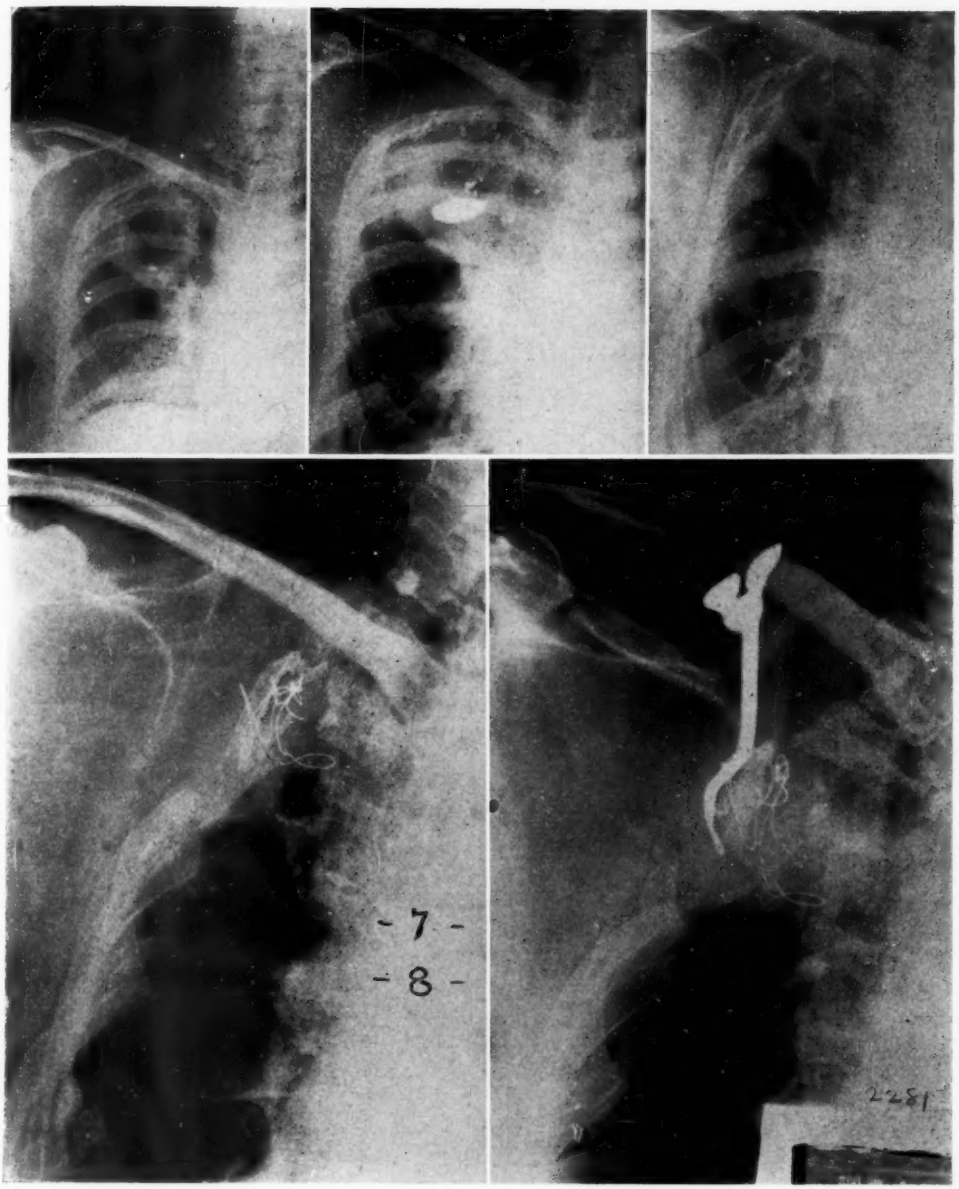


FIG. 1a. (Upper left.) Mrs. R. B. February 7, 1939. Cavity displaced downwards after apical thoracoplasty.

FIG. 1b. (Upper center.) Mrs. R. B. March 25, 1940. Cavity filled with lipiodol.

FIG. 1c. (Upper right.) Mrs. R. B. April 9, 1941. Cavity persists after further rib resection.

FIG. 1d. (Lower left.) Mrs. R. B. November 22, 1941. Small residual cavity persists after two thoracoplasties, suction drainage and osteoplastic revision operation.

FIG. 1e. (Lower right.) Mrs. R. B. January 26, 1942. Cavity not demonstrable eight months after osteoplastic thoracoplasty.

FIG. 2a. (Upper left.) Mr. R. C. April 3, 1941. Large apical cavity with tuberculous bronchial stenosis.

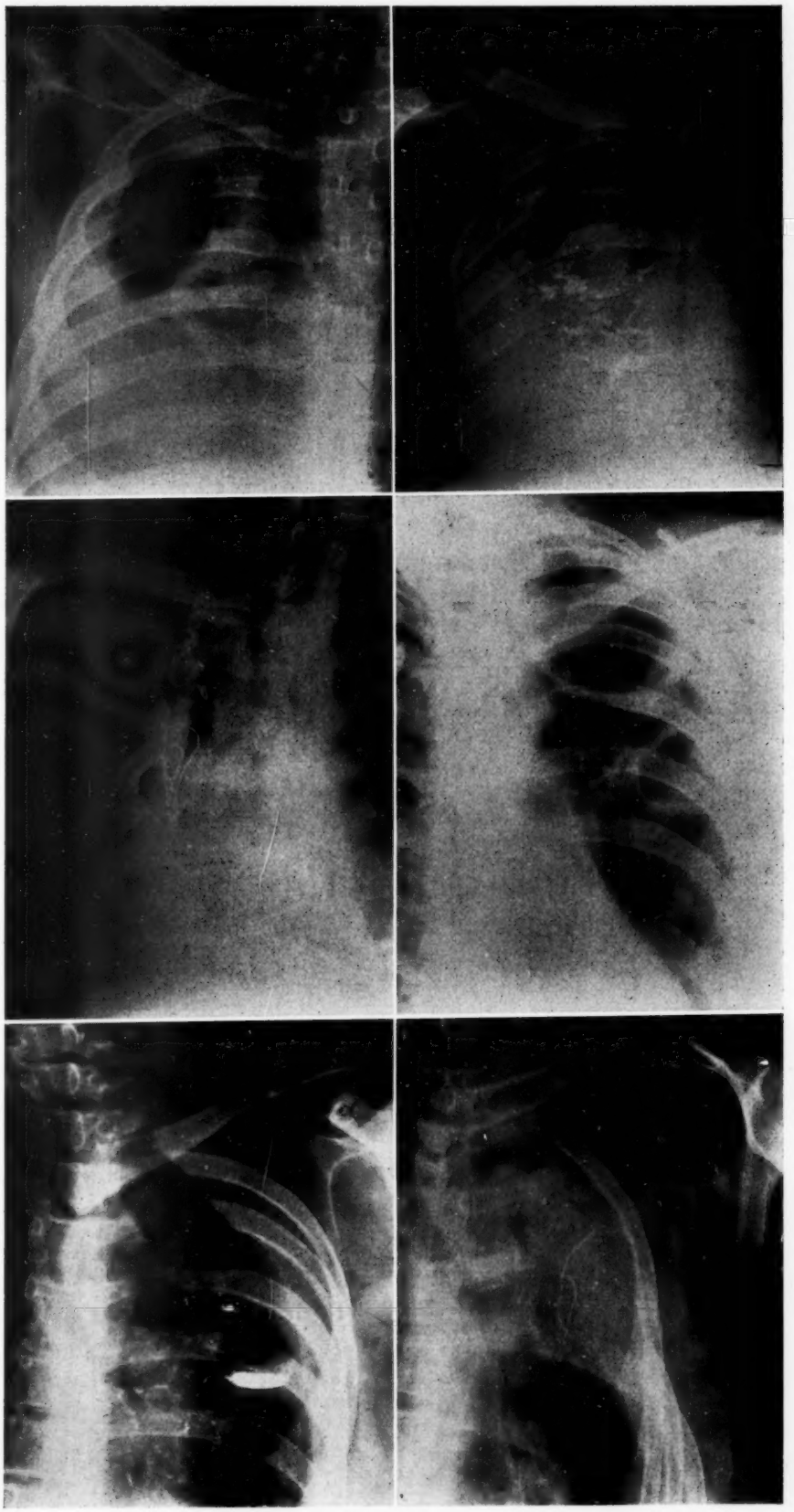
FIG. 2b. (Upper right.) Mr. R. C. July 17, 1941. Cavity smaller after apical thoracoplasty. Basal bronchiectasis.

FIG. 2c. (Center left.) Mr. R. C. February 10, 1942. Cavity smaller but still demonstrable after two osteoplastic thoracoplasties.

FIG. 3a. (Center right.) Mrs. I. D. November 20, 1940. Two large inflated apical cavities.

FIG. 3b. (Lower left.) Mrs. I. D. June 30, 1941. Upper cavity not demonstrable, but lower cavity (lipiodol injection) persists after apical thoracoplasty.

FIG. 3c. (Lower right.) Mrs. I. D. August 20, 1941. Osteoplastic thoracoplasty with braided wire loop (which has broken). Cavities no longer demonstrable one month after operation.



FIGS. 2a–3c

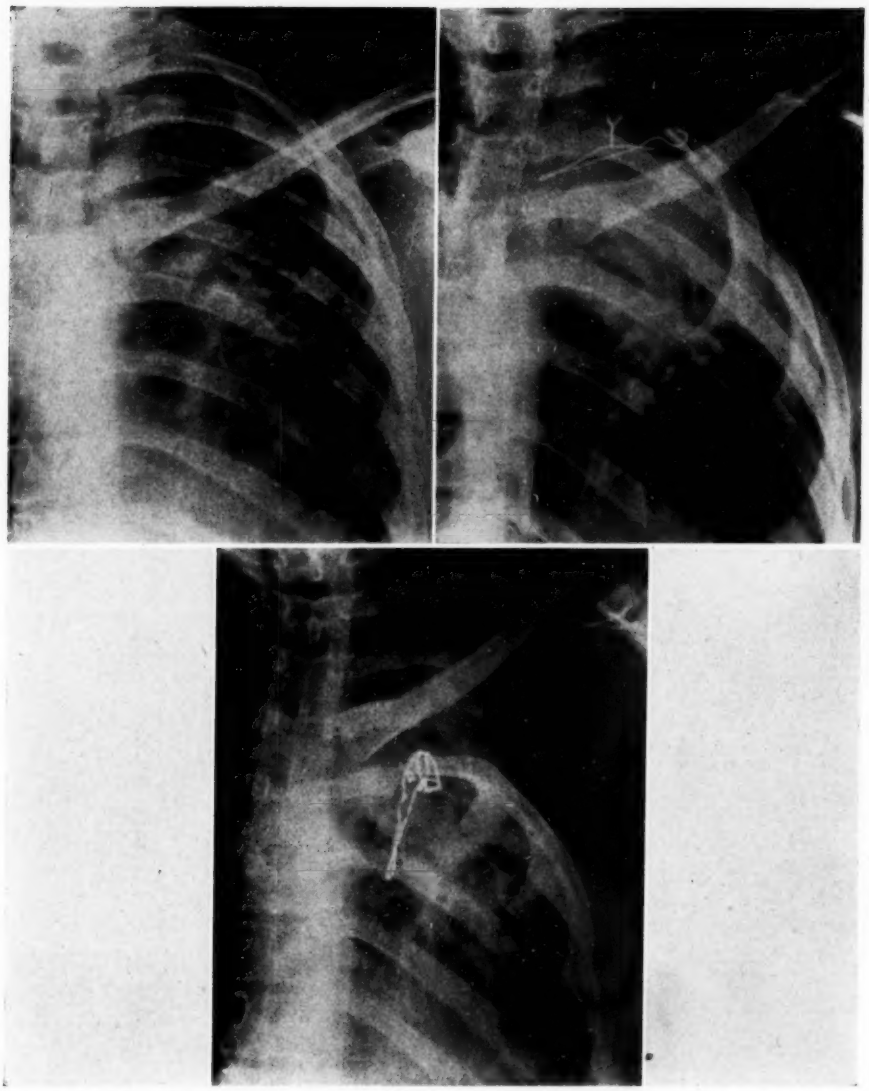


FIG. 4a. (Upper left.) Miss L. T. January 12, 1942. Multiple cavities with one large one in fifth intercostal space.

FIG. 4b. (Upper right.) Miss L. T. February 3, 1942. Apical osteoplastic thoracoplasty. Wire loop has broken. Large cavity not seen.

FIG. 4c. (Lower center.) Miss L. T. March 6, 1942. Reoperation, second osteoplastic thoracoplasty. Effective compression of upper left chest.

FIG. 5a

FIG. 5b

FIG. 5a. Diagram of osteoplastic thoracoplasty in which the anterior stump of the second rib is wired to the posterior portion of the fourth rib at its articulation with the transverse process.

FIG. 5b. Diagram of operation in which the second rib is rotated 180° (so that its convexity looks inwards) and its free end is pushed through the fourth intercostal space and wired under the fourth rib at its junction with the transverse process.

EXTRAPLEURAL PNEUMONOLYSIS WITH PACK[1]

RALPH C. MATSON

In this second contribution, which is also preliminary to a full presentation of my material and experience now in the course of preparation, I shall neither go into the chronology nor a discussion of the various operative procedures proposed from time to time for the closure of tuberculous cavities by means of extrapleural stripping with various types of fills, either as a reconstruction thoracoplasty or as a primary procedure in lieu of thoracoplasty. To enumerate some of the different types utilized: Tuffier employed a fill of fat; Baer used paraffin; Morrison Davies, Sebrechts, Alexander and Archibald used muscle; Lilienthal applied a rubber dam; Oughterson and Hawen utilized rubber bags; Mikulicz, Schlange, Sauerbruch and Kinsella inserted gauze packs.

The purpose of this contribution is to describe its present technique and report the results of the operation which I have proposed.

In 1935, I proposed, and later reported,[2] a method for the closure of residual pulmonary cavities after thoracoplasty by means of an extrapleural pack. It was found to be simpler and more effective than removal of regenerated rib in a reconstruction thoracoplasty and the results suggested its possible effectiveness when employed as a primary procedure in certain selected cases. Since 1935, 81 cases have been operated upon by this method.

The operation consists of an extrapleural stripping, as in extrapleural pneumothorax. Then, instead of accomplishing a collapse of the lung by air or oil refills, as in extrapleural pneumothorax, I accomplish a selective collapse of the area desired by means of a pack which is formed by lining the extrapleural space with flexi-tissue and filling the sack, thus created, with gauze, according to the technique later described.

The collapse obtained by this operation is truly selective, because Bucky films, tomographs and opaque oil studies reveal the size and location of the cavities to be closed and pressure can be exerted directly over these areas by a semi-solid insert, thus producing a type of compression unobtainable by air or oil refills. There is little or no dissipation of pressure or uninvolved areas, which is so common after extrapleural pneumothorax.

The operation is not shocking and is as well tolerated as extrapleural pneumothorax. It accomplishes the aim of thoracoplasty or apicolysis and, while technically more difficult than extrapleural pneumothorax, it accomplishes the same purpose as all three above methods. But unlike thoracoplasty, the collapse is reversible, which may be objectionable in some cases, as in extrapleural pneumothorax. However, it has the advantage over the latter in that it is selective and postoperative management simpler, as no refills of air or oil

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[2] Bulletin of the American Academy of Tuberculosis Physicians, November, 1938.

are necessary and the patient may return home within a comparatively short time after operation.

INDICATIONS

This operation was originally proposed for the closure of residual cavities remaining after thoracoplasty, in place of the tedious and often ineffectual method of removing regenerated bone to secure a better collapse of the lung. Later, its indications were extended to certain selected cases in preference to thoracoplasty. However, the operation was never proposed as a substitute for thoracoplasty. Obviously, all cases subjected to the operation had presented indications for some form of collapse therapy, and artificial pneumothorax had been attempted unsuccessfully—either no free pleural space was found, or the pneumothorax was unsuccessful because of the presence of adhesions which were unsuited for intrapleural pneumonolysis. In general, it has been employed as a primary procedure in those cases where extrapleural pneumothorax would have been the logical procedure to utilize—that is, in cases of tuberculous cavities or areas of infiltration in either one, or both, upper lung fields.

The best results will be obtained in apical, or subapical, comparatively recent soft-walled cavities of not more than 4 or 5 cm. in diameter, preferably with little or no pericavity infiltration, not too peripheral and with a patent drainage bronchus.

From the standpoint of their type of lesion, many of my cases might have been considered candidates for a radical apicolysis or partial thoracoplasty. However, their general condition was such that it was doubtful whether the patient could withstand the more traumatizing type of operation.

The indications for this operation are by no means definite. Added experience and time will clarify the selection of cases. A thoracoplasty or artificial pneumothorax on the opposite side is no contraindication providing there is a satisfactory vital capacity.

PREOPERATIVE PREPARATION

A week or more before operation the patient is allowed up-time in order to increase the cardiovascular tone, unless there is some contraindication. Exercise up to two hours per day is permitted, provided there are no complications. Sputum volume determinations are made daily up to the day of operation. The patient is encouraged to raise the usual twenty-four-hour quantity before going to the operating room. The operation is usually performed in the afternoon when drainage is more likely to be complete. The vital capacity is determined and an electrocardiogram taken. In one case, an abnormal electrocardiogram became normal after operation, due to relief of mediastinal displacement. Nembutal grains one and one-half and pantopon grain one-third is given three-quarters of an hour preoperatively and avertin 60 to 70 mg. per kilo instilled into the rectum twenty minutes before surgery. The patient is placed in an anterolateral prone position with the scapula on the side to be operated displaced well laterally, as the posterior approach is usually used.

TECHNIQUE

Light anaesthesia is employed, with nitrous oxide and helium. The skin and subcutaneous tissues are infiltrated with 1 per cent novocain-suprarenin solution and a four inch longitudinal incision made over the rib to be resected—usually the third or fourth. The trapezius and rhomboid muscles are split and novocain

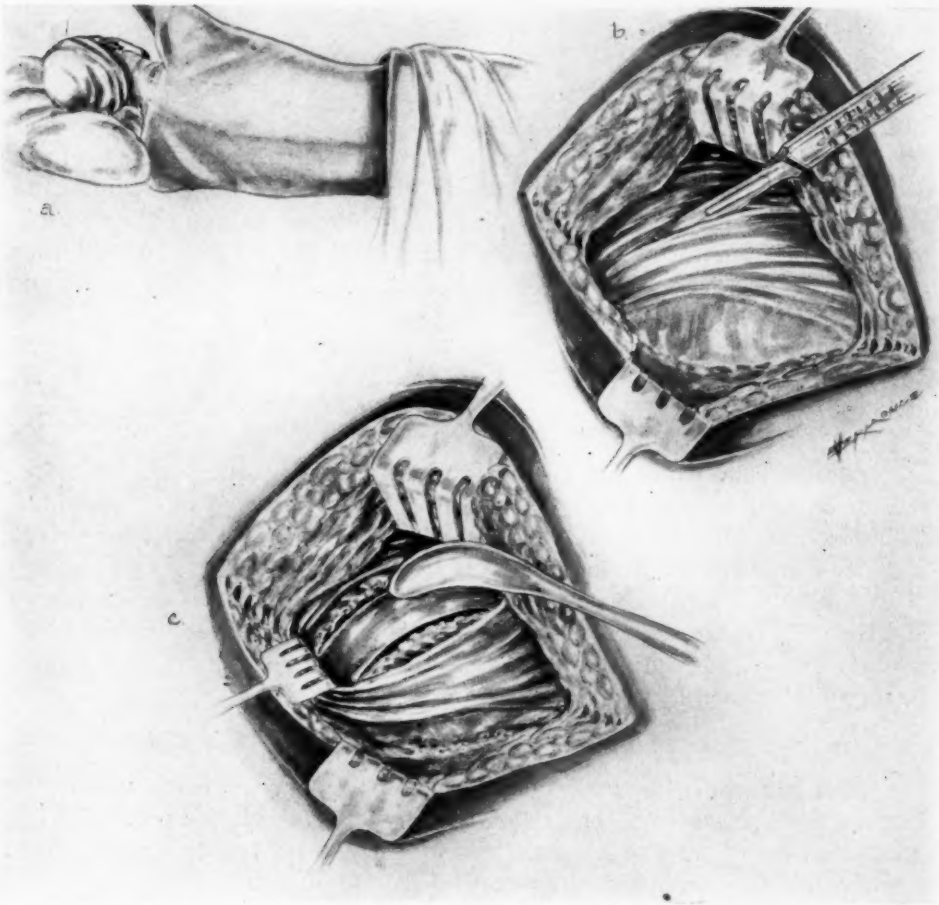

FIG. 1. a: Position of patient on table. b: Incision through the serratus posterior superior muscle. c: Exposure of the rib and stripping of its periosteum.

solution injected into the intercostal space above and below the rib to be resected (figure 1). A three inch section of the rib is removed in the usual manner. The extrapleural space is entered at a point of attachment of the external intercostal muscle and periosteum of the rib-bed by means of a flat raspatory and stripping begun with the finger. From this point on, the separation of the lung from the chest wall is performed under direct vision by means of Overholt illuminated retractors and Cameron lights. The lung is stripped by means of

small pill or pea sponges on Overholt forceps and bleeding controlled by the high frequency coagulating current, which is preferable to metal clips. As the apex and subclavian bed is approached, stripping is made toward the mediastinum and carried downward along the mediastinal surface as far as is deemed necessary or safe.

After the extrapleural space has been developed to suitable dimensions, all bleeding is controlled and the space irrigated with warm normal saline and suc-

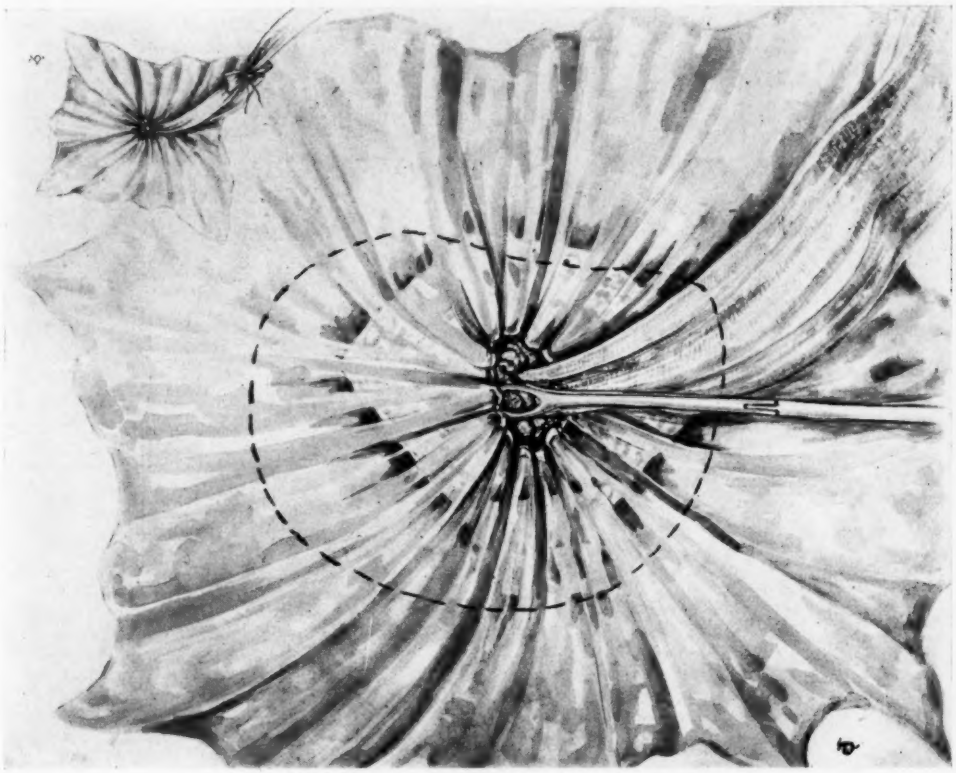

FIG. 2. a: Dotted line indicates extent of pocket on posterior chest wall. Gauze is being packed into the flexi-tissue sack by means of sponge forceps. b: Showing gauze bandages tied together while being packed into sack.

tioned dry. A sheet of flexi-tissue two feet square, previously sterilized by soaking it in mercuric cyanide solution 1:1,000 for thirty minutes or more, is rinsed in sterile water and inserted into the extrapleural space with a sponge forceps in such a manner as to completely line the inner chest wall and surface of the stripped lung (figure 2).

The packing consists of one, two or three inch gauze bandage (depending upon the size of the space to be filled) tied end on end with No. 6 deknatol and soaked in the following solution: 8 oz. physiological saline solution mixed

with enough castile soap to make a good lather. To this mixture is added 10 drams vioform powder, 1 dram pure carbolic solution and 1 oz. of glycerine. After thoroughly soaking the bandages, they are removed from solution and allowed to dry for at least twelve hours; they are placed in jaws and autoclaved for thirty minutes at 20 pounds pressure.

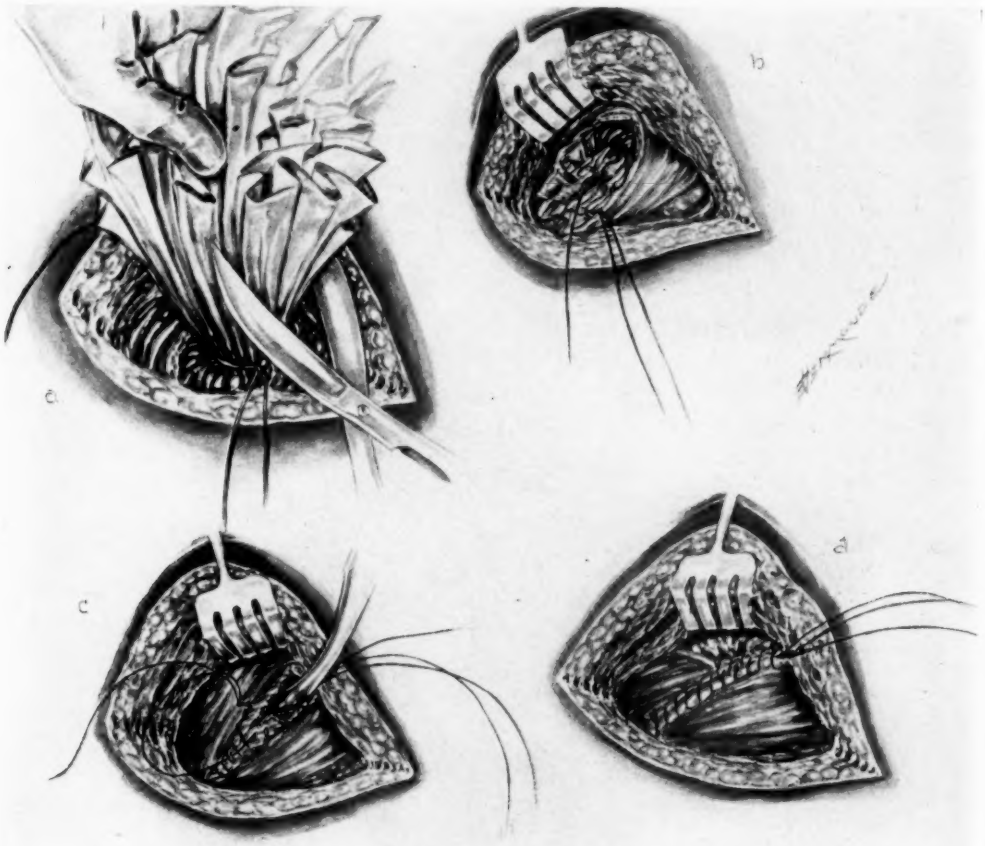

FIG. 3. a: Showing deknatol tie around the neck of the sack and severing of the flexitissue distal to the tie. b: Showing severed neck of the sack ready to be buried in the extrapleural space. c: Raspatory pushing neck of sack in extrapleural space while the serratus posterior superior muscle is being closed. d: Completed suturing of the serratus posterior superior muscle.

Then, by means of the sponge forceps, the gauze packing is introduced into the sack in a circular manner so that the deepest parts are filled first and then the dome of the stripped lung is gently compressed with gauze packing until the space is semi-solidly packed to the level of the chest wall.

After the sack has been completely filled, a short No. 6 deknatol tie is placed on the end of the gauze to facilitate its removal and dropped back into the sack. The neck of the sack is grasped in the hand and two heavy curved haemostats

placed distal to the gauze level to partly close it. The sack is tied as tightly as possible with two No. 6 deknatol ligatures as the clamps are slowly removed. About three-quarters of an inch of stump is allowed to remain. This is then pushed into the extrapleural space away from the chest wall opening. If the parietal pleura strips away very easily and further spontaneous separation might take place because of the weight of the sack (which, after all, is less than nearly any other fill), a chromic gut suture is passed through the neck of the sack distal to the tie and brought around the rib above the chest wall opening and tied (figure 3).

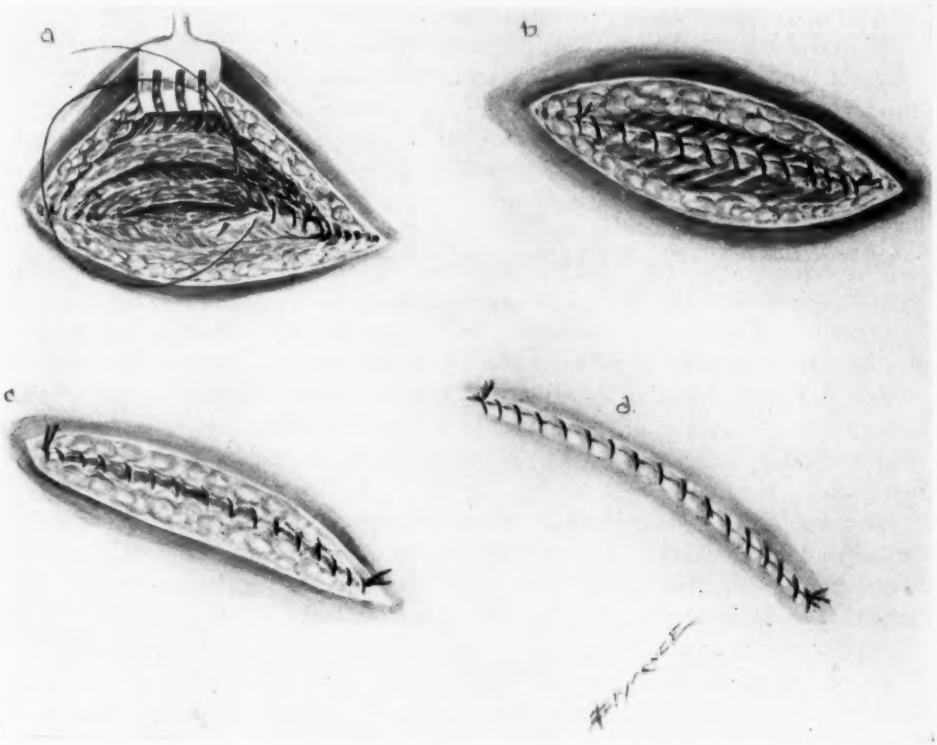

FIG. 4. Further steps in closure of the wound without drainage

The muscles are approximated in layers and the fascia and skin closed without drainage (figure 4).

The technique for its use in reconstruction thoracoplasty is identical except that one must prepare an opening through the bed of regenerated bone. Or, in case of partial thoracoplasty, the approach is best made through the rib bed of the uppermost unresected rib.

POSTOPERATIVE CARE

The patient is placed in an oxygen tent for twenty-four hours, or carbogen is given for fifteen minutes every two hours to promote hyperventilation and

coughing and the patient turned frequently from side to side. A transfusion of 300 to 500 cc. of citrated blood is given immediately after operation, if necessary. Opiates are used sparingly except when there is severe pain.

The wound is inspected in twenty-four hours and sutures removed from the fifth to seventh day.

COMPLICATIONS

There is usually a mild postoperative reaction manifested by slight elevation of temperature for a few days. Of my series of 81 cases, no exudate occurred in 39 cases. In 24 cases serous exudate occurred, and in 18 cases a purulent exudate formed sooner or later—in 16 of these it was necessary to remove the pack.

In several instances a sizable effusion occurred which separated the remaining lung from the chest wall. Here, the pack was removed and the space converted into an extrapleural pneumothorax. In others, a mild serous effusion around the pack occasionally required a small incision in the operative wound for drainage. This rarely is a serious event. Should the fluid become infected, irrigations with Dakin's or azochloramid solution around the pack usually control it.

REMOVAL OF THE PACK

The pack should be allowed to remain as long as possible (one and one-half to three years) to control the underlying lesions. (One patient has had three separate packs in position now over four and one-half years.) Should any complication occur demanding its removal, this is quickly accomplished under local anaesthesia. To maintain the space, it is then converted into an extrapleural oleothorax. If this is not done, it is surprising how rapidly the space becomes obliterated.

In uncomplicated cases, the date of removal depends upon the condition of the underlying lung. An inadequate pack may frequently be supplemented by one in another position, the wall of the extrapleural space having been differentiated from that of an unclosed cavity by radio-opaque studies.

In removing the pack, an incision is made down to the bed of the resected rib. If the rib has regenerated, a small section is removed. The sack is grasped with an Allis forceps and a stab incision made through the sack. A large crochet-hook is inserted into the pack as near the neck as possible and the deknatol loop at the end of the gauze is engaged and the gauze withdrawn. The flexi-tissue is then removed intact. It is not necessary to sever the neck ligatures. After inspecting the remaining space and it has been definitely demonstrated that a bronchopleural fistula is not present, it is irrigated with warm normal saline and the wound closed without drainge.

Closure of the extrapleural space may result by reëxpansion of the lung and may occur in a matter of days. In others, the space fills with a sterile exudate that may become organized and obliterate the space by expansion of the lung and contraction of the chest wall. In still others, a permanent air pocket remains.

RESULTS

In reviewing my series of 81 cases, all with a positive sputum, 54 cases were converted to negative. The sputum remained positive in 27 cases; 15 cases are reported as clinically well with packs removed; 49 cases still have packs in position and, of these, 39 have a negative sputum.

There were no deaths directly due to the operation. One death was due to a blood transfusion reaction; one due to an aspiration bronchopneumonia following haemoptysis, and 2 were caused by the independent progressive evolution of the disease in spite of the operation.

CONCLUSIONS

The operation described is not proposed to replace thoracoplasty, but rather to be applied in cases where extrapleural pneumothorax comes into question. While the technique is more complicated, it is at least more selective. Compression of cavities may be obtained by the pack operation which would be unobtainable by refills of air or oil injection. Moreover, the after-care is simple as no refills of air or oil are required.

In certain cases, where thoracoplasty is indicated, the pack operation has the advantage in that it is a reversible procedure and can be utilized in poor surgical risks. Another advantage is that the period of hospitalization is incomparably shorter than after thoracoplasty.

The complications are the same as obtain in extrapleural pneumothorax and the extrapleural space, after the pack is removed, conducts itself in the same manner as a discontinued extrapleural pneumothorax.

A partial thoracoplasty may be required in a certain number of cases, following removal of the pack.

Judgment as to its ultimate value must be reserved until we know more about the causes of late exudate formation. However, there is sufficient evidence, according to our experience, that the operation has a definite place, although possibly a small one, in surgical collapse therapy.

CONCLUSIONES

La operación descrita no se propone suplantar la toracoplastia, sino más bien su aplicación en los casos en que hay dudas sobre el neumotórax extrapleural. Aunque la técnica es más complicada, es por lo menos más selectiva. Esta operación permite obtener una compresión de las cavernas que no lograría la repetición de las inyecciones de aire o de aceite. Además, el cuidado postoperatorio es sencillo, pues no se necesitan más rellenos.

En ciertos casos en que está indicada la toracoplastia, la nueva operación posee la ventaja de que es un procedimiento invertible y puede utilizarse en los malos riesgos quirúrgicos, siendo otra ventaja que el período de hospitalización es incomparablemente más breve.

Las complicaciones son idénticas a las observadas en el neumotórax extra-

pleural, y el espacio extrapleural, después que se elimina el tapón, actúa en la misma forma que un neumotórax extrapleural suspendido.

En cierto número de casos puede necesitarse una toracoplastia parcial después de extraer el empaque.

Hay que reservar el juicio definitivo hasta que conozcamos mejor las causas de la formación tardía de exudados, pero ya hay suficientes datos indicativos de que la operación tiene su puesto propio, aunque posiblemente pequeño, en la colapsoterapia quirúrgica.

PULMONARY COCCIDIOIDAL DISEASE[1,2]

ROBERT A. PEERS, EMILE F. HOLMAN AND CHARLES EDWARD SMITH

The protean character of coccidioidal infection would necessitate a monograph for any reasonably complete presentation. We are limiting this paper to a discussion of clinical types in which pulmonary involvement is demonstrable and prominent. Exceptionally the portal of entry may be the skin rather than the respiratory tract. Much more frequently cutaneous, meningeal, subcutaneous or bone and joint lesions may develop without clinical or roentgenographic evidence of a pulmonary lesion. Even at autopsy, a coccidioidal focus may be overlooked by anyone other than a pathologist who is skilful, experienced and on his guard. One must appreciate that many primary coccidioidal infections occur without demonstrable roentgenographic changes, even though proof through recovery of the fungus from the sputum cannot be challenged. Sometimes clinical symptoms are completely lacking and the proof of infection lies in the change in reaction of the coccidioidin test. There is no reason to doubt but that these are respiratory tract infections. We are presenting this series because of their frank pulmonary involvement. In each case *Coccidioides immitis* was recovered from the sputum or the pleural fluid and there was ample roentgenographic evidence of an extensive nature. The extreme difficulty of differentiating these cases of coccidioidomycosis from tuberculosis on a clinical basis is readily apparent.

PRIMARY COCCIDIOIDOMYCOSIS WITH ERYTHEMA NODOSUM

"San Joaquin Fever," "Valley Fever," "Desert Rheumatism" etc.

The first case typifies primary coccidioidal infection. We now recognize that probably only one person in from twenty to fifty (1) who experience this infection has erythema nodosum. However, it was recognition of the aetiology of "San Joaquin fever" by Gifford (2, 3) and by Dickson (4, 5, 6) which marked a new era for coccidioidal investigation.

C. Y., a ten year old white American girl, was brought to Doctor Lipson and Doctor Falk, of Visalia, on January 10, 1938, because of red lumps on the legs and painful ankles of eighteen days' duration.

Born in Oklahoma, the patient came to Tulare County, in the San Joaquin Valley of California, in June, 1937, with her parents, a seven year old sister and a two months old brother. The family worked on a cotton ranch and dust was everywhere. Moreover, the family lived in a tent pitched on the concrete floor of a dusty barn.

On December 18, 1937, the patient developed a severe respiratory infection with fever, sore throat, racking cough, generalized aching and severe pain in the left chest. The sore throat diminished but the other symptoms continued. On December 23, 1937,

[1] From the Colfax School for the Tuberculous, Colfax, California, and the Stanford University School of Medicine, Departments of Surgery and of Public Health and Preventive Medicine, San Francisco, California.

[2] This study was aided by grants from the Rosenberg Foundation.

red nodules appeared on the fronts of both legs and the ankles became very painful. The nodules continued to come in crops and, on January 19, 1938, the parents sought medical aid.

Examination revealed a pale, rather thin girl of ten who limped as she walked and who coughed frequently. Her temperature was 98.6°F. in the morning of January 10 and was 99.2°F. at noon two days later when one of us saw her. The chest was entirely clear. The only positive physical findings were typical coppery red, extremely tender nodules on the anterior surfaces of both legs and extending above the knees to the lower third of the thighs. The lesions on the legs were 3 to 7 cm. in diameter. Those on the thighs were 1 to 2 cm. in diameter. The ankles were slightly swollen, not red, quite tender to pressure and painful on motion.

The coccidioidin reaction (0.1 cm. of 1:1,000 dilution intracutaneously, performed January 10) measured 40 x 30 mm. of induration in forty-eight hours with a central bleb 15 mm. in diameter. Mantoux test (1.0 mg. of OT) was negative. Sputum was collected January 13 and *Coccidioides immitis* was recovered both culturally and by animal inoculation.

A roentgenogram taken January 10 (figure 1A) showed enlarged hilar nodes and, in the left upper chest, an area of increased density extending as a band from the hilum to the chest wall.

The patient improved rapidly. The cough and pleurisy lasted until January 15 and the erythema nodosum and arthritis were painful until January 20, 1938. Another roentgenogram taken January 28 (figure 1B) showed very considerable clearing. The family migrated again and additional follow-up was impossible.

Comment: Only six months after her arrival in the San Joaquin Valley and at the end of the dusty season, this patient underwent an attack of primary coccidioidomycosis. One may note that the winter rains began on December 8—her onset was December 18 and the usual incubation period is ten to sixteen days (1, 7). Her recent arrival and her dusty environment illustrate previously reported epidemiological points (1, 3). Her clinical picture is likewise typical. First we observe malaise, fever, cough and severe pleural pain without significant physical findings in the chest. This comprises the illness seen in most severe primary coccidioidal infections. Then, after an interval of five days, we witness the second phase—that of erythema nodosum, which constitutes so-called "San Joaquin fever" or "Valley fever." Arthritis, seen in this patient, is frequently concomitant with the erythema nodosum and, on the west side of the San Joaquin Valley, often gives rise to the name "desert rheumatism." As in this

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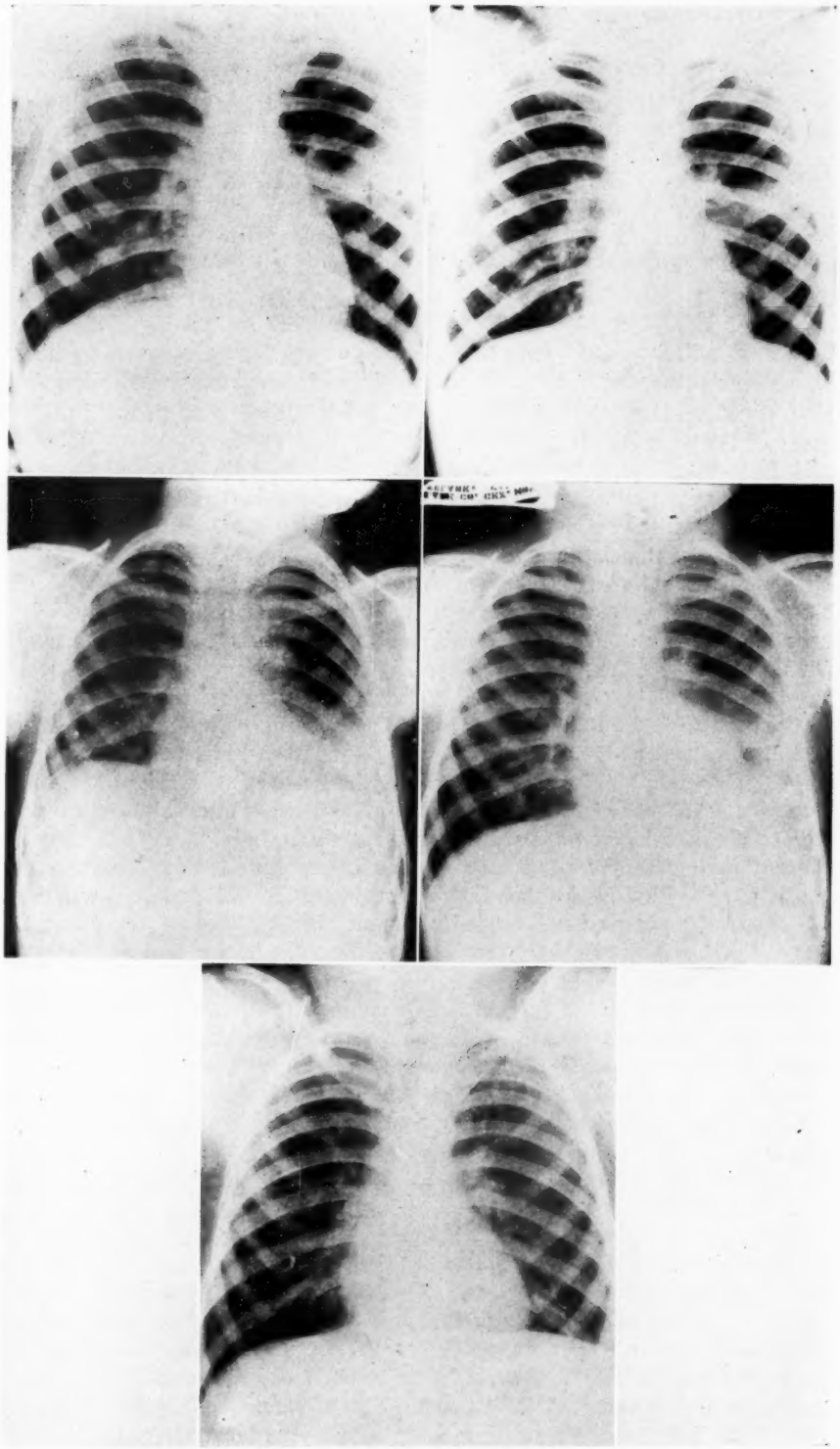
FIGS. 1A upper left and B upper right. Patient C. Y., with primary coccidioidal infection and erythema nodosum ("San Joaquin fever"). *A* was taken January 10, 1938, twenty-three days after onset of symptons, and *B*, nineteen days later, on January 29, 1938. Note rapid regression within that interval.

FIGS. 2A center left, B center right and C lower. Roentgenograms of patient L. M. with pleurisy with effusion due to *Coccidioides immitis*. *A* was taken March 16, 1938 as fluid was forming. *B* was taken March 31, 1938 (two weeks later), ten days after 200 cc. of pleural fluid had been removed. *C* was taken November 1, 1938 (seven months later) and shows complete absorption of the fluid. Hilar shadows are large although patient was tuberculin-negative.



FIGS. 1A–2C

illustrative case, the second spectacular phase is more common in females (1, 3) but, as has been emphasized, is relatively infrequent in the total of all coccidioidal infections (1, 11). The vigor of the coccidioidin reaction in this patient is characteristic of the hypersensitivity of "San Joaquin fever" patients (2). It recalls the belief that erythema nodosum is an allergic manifestation in coccidioidal infections as it is in other conditions (1, 6). The roentgenographic mimicry of primary tuberculosis and the rapid clearing are likewise noteworthy.

PLEURISY WITH EFFUSION DUE TO COCCIDIOIDES IMMITIS

The next patient illustrates an occasional complication of coccidioidal infection. When it occurs, in relation to the time of the primary infection, is difficult to decide. However, in this case, at least, the effusion probably occurred as part of that very illness.

L. M., a six year old white American school boy, entered Tulare General Hospital March 16, 1938, with complaint of pain in the left upper abdomen and lower chest of two days' duration and a "cold" and sore throat of ten days' duration.

Born in Colorado, the patient came to a large ranch near Tulare, California, on June 27, 1937 (seven and one-half months prior to his present illness). The family lived in an unkempt single-room cabin. The grounds were bare and he played in the dirt a great deal.

On March 6, 1938, the patient developed a "chest cold" and cough, accompanied by a sore throat. This respiratory infection did not seem remarkable and, as he did not seem feverish, no medical aid was sought. After a week, the infection seemed to have subsided. The patient went to bed on the night of March 14 feeling entirely well. He awakened during the night with severe pain in the lower left chest and upper abdomen and seemed feverish. During the next two days his condition grew worse and, on March 16, he was taken to the Tulare General Hospital.

Physical examination at entry revealed an acutely ill and dyspnoeic boy whose nasal alae dilated with inspiration. His temperature was 102.8°F., his throat was reddened but his chest was reported as clear and resonant. His white count, on March 17, was 15,350 with 74 per cent polymorphonuclear neutrophils, 22 per cent lymphocytes and 4 per cent monocytes.

The fever and pleuritic pain persisted. On March 18 the voice sounds were decreased at the left base but no râles (then or later) were heard. As the roentgenogram (figure 2A) shows, the left base was hazy. By March 20 dulness was definite and two days later signs of fluid in the left chest were unmistakable. On this day, by thoracentesis, 200 cc. of yellow opalescent fluid were removed (specific gravity 1.020, many pus and endothelial cells). *Coccidioides immitis* was recovered from the pleural exudate.

The patient remained in the hospital until April 2, 1938. His temperature had gradually fallen to 99.4°F. and he was discharged. The roentgenogram, taken March 21, (figure 2B) indicates that fluid was still present.

He was kept in bed for a week after his discharge and then was allowed to play as usual. He was slow to regain weight. When visited June 1, 1938, he had just caught cold—a typical coryza. His temperature was 99.4°F. He had no pain in the chest. The physical examination of the chest was entirely normal. A sputum examination failed to reveal *Coccidioides*. A coccidioidin test (0.1 cc. of 1:1,000 dilution intracutaneously), performed June 1, 1938, measured 21 x 15 mm. of induration at twenty-four hours and 25 x 25 mm. at forty-eight hours. The Mantoux test of 0.1 mg. OT was

negative. The mother failed to react to coccidioidin and to tuberculin in these same amounts.

The mother was urged to take the boy back to the hospital for a recheck of the roentgenogram. The family did not heed the advice and a follow-up visit was made September 15, 1938. The patient looked fine, had a normal temperature, had gained weight and was attending school. It was just too much trouble to take him for a recheck. Finally, in November, 1938, more as a favor to us than as a safeguard to the lad, the mother brought him in for his roentgenogram, which, except for large hilar nodes, appeared quite normal (figure 2C). The family had moved on when another visit was made in the spring of 1939.

Comment: Occasionally pleural effusion caused by *Coccidioides* is extensive. That it is part of the initial infection is supported by the fact that a small collection of fluid in the costophrenic angle of the diaphragm is sometimes seen in roentgenograms of patients with severe primary coccidioidomycosis. The prognosis is usually very satisfactory. This patient recovered completely although he was not given anything approaching proper care. The same was true of several other patients whom we have observed. On the other hand, pleural effusion may occur in patients who plunge directly into coccidioidal granuloma. It may be significant that L. M. and all the others who absorbed their effusions without apparent complications were very sensitive to coccidioidin. On the other hand, patients who have pleural effusions as they develop fatal coccidioidal granuloma react weakly to coccidioidin. Moreover, the former have all been whites, the latter usually Filipinos or others of the dark-skinned races. These observations are made on too few cases to be very certain of one's ground, but they are in line with sensitivity in coccidioidomycosis (1, 2).

PULMONARY CAVITY IN COCCIDIOIDOMYCOSIS

We are presenting the histories of two patients who had solitary cavities caused by *Coccidioides immitis*. It will be apparent that these patients do not fit into our old conception of disseminating coccidioidal granuloma, even though analogy with tuberculosis would incline one toward this belief.

Mrs. W. S., a twenty-five year old white American housewife, referred to the Stanford Clinic on August 4, 1938, for coccidioidal granuloma, complained of pain in the back and blood in the urine since July 20, 1938. She had been to the San Mateo Clinic where a preliminary investigation of the urinary tract by Dr. H. L. Mawdsley failed to reveal the cause of the haematuria. However, Dr. W. F. Knorp, of the San Mateo Clinic, eliciting a history of "Valley fever," had roentgenograms taken of her chest which revealed a cavity in her right upper lobe. He found that she reacted to coccidioidin and had *Coccidioides immitis* in her sputum.

Born in Texas, she came to Coalinga, California, in 1927, to be with her tuberculous sister, who died the following year. The patient reached the arid slopes of the western San Joaquin Valley in August and, in October, had an attack of "desert fever" (erythema nodosum). She recovered without incident and, in 1931, married. Children were born in the succeeding two years and she felt run down. In 1936 she had a haemorrhage for three days, which her local physician told her came from her lungs although no roentgenograms were taken. She did not remain in bed long but continued her energetic life as

housewife and mother without recurrence of haemoptysis. She had several attacks of pain in the right side radiating to her back and groin. In January and March, 1938, she had several illnesses beginning with cold in the head and continuing for a week with generalized aches, chills, fever, cough and slight pain in the right chest. Then, on July 20, 1938, while on a trip to the Coast, she began having moderately severe, though not cramping, low back pain, worse on the right side. These symptoms lasted a week and were followed by bloody urine for a week. There was no fever, frequency, burning or nocturia but some nausea and occasional vomiting. The haematuria returned for three days early in August but has never returned.

Physical examination revealed a thin but healthy appearing young woman in no apparent discomfort. The only positive findings were fine râles over the right apex posteriorly and an incidental cervical erosion.

Cystoscopy showed normal bladder and ureters with intravenous indigo-carmine appearing promptly from both ureters in good concentration. Retrograde and intravenous pyelograms were normal. Urine showed a faint trace of albumin and 10 erythrocytes per high dry field. Addis concentration test was normal, except for 600 million red cells and 240 mg. of protein in twenty-four hours. (Tests made on subsequent visits were normal.) Twelve samples of urine, which were cultured and inoculated into guinea pigs over a period of four months, failed to reveal *M. tuberculosis* or *Coccidioides immitis*. Blood urea was 55.5 mg. per cent.

Blood contained 3.06 million erythrocytes and 58 per cent haemoglobin (Sahli.). There were 10,360 leucocytes with 54 per cent neutrophils (5 per cent banded), 4 per cent eosinophils and 42 per cent lymphocytes. The erythrocyte sedimentation rate was 19 mm. in sixty minutes (Wintrobe method, corrected.)

Coccidioidin reaction (0.1 cc. of 1:1,000 dilution intracutaneously) measured 25 x 30 mm. of induration and tuberculin reaction (0.01 mg. OT) measured 10 x 10 mm.

Coccidioides immitis was recovered from the sputum culturally and by animal inoculation.

Roentgenograms of the chest revealed the outline of a very thin walled cavity (figure 3A) which required lipiodol to delineate it satisfactorily (figure 3B). The lipiodol ran into the main bronchus of the right upper lobe and immediately into a large cavity which lay far posteriorly. This cavity measured about 6 x 2 x 3.5 cm. It appeared to be unilocular. When the patient was put in the upright position, lipiodol drained out of it readily and ran into the lower lobe bronchus. The absence of infiltration around the cavity was especially noteworthy.

The patient was discharged from the hospital with the diagnosis of "coccidioidal granuloma, pulmonary, with cavitation; haematuria, unexplained." Incidentally, the haematuria never has been explained.

She was discharged to the care of the Fresno General Hospital and the services of Dr. Henry A. Randel, with the recommendation that pneumothorax be instituted and that she be given enteric coated thymol capsules and iron, orally. These measures were carried out. Within four months her blood urea had fallen to 33 mg. per cent, her haemoglobin had risen to 89 per cent (Sahli) and her erythrocytes to 4.6 million. She took

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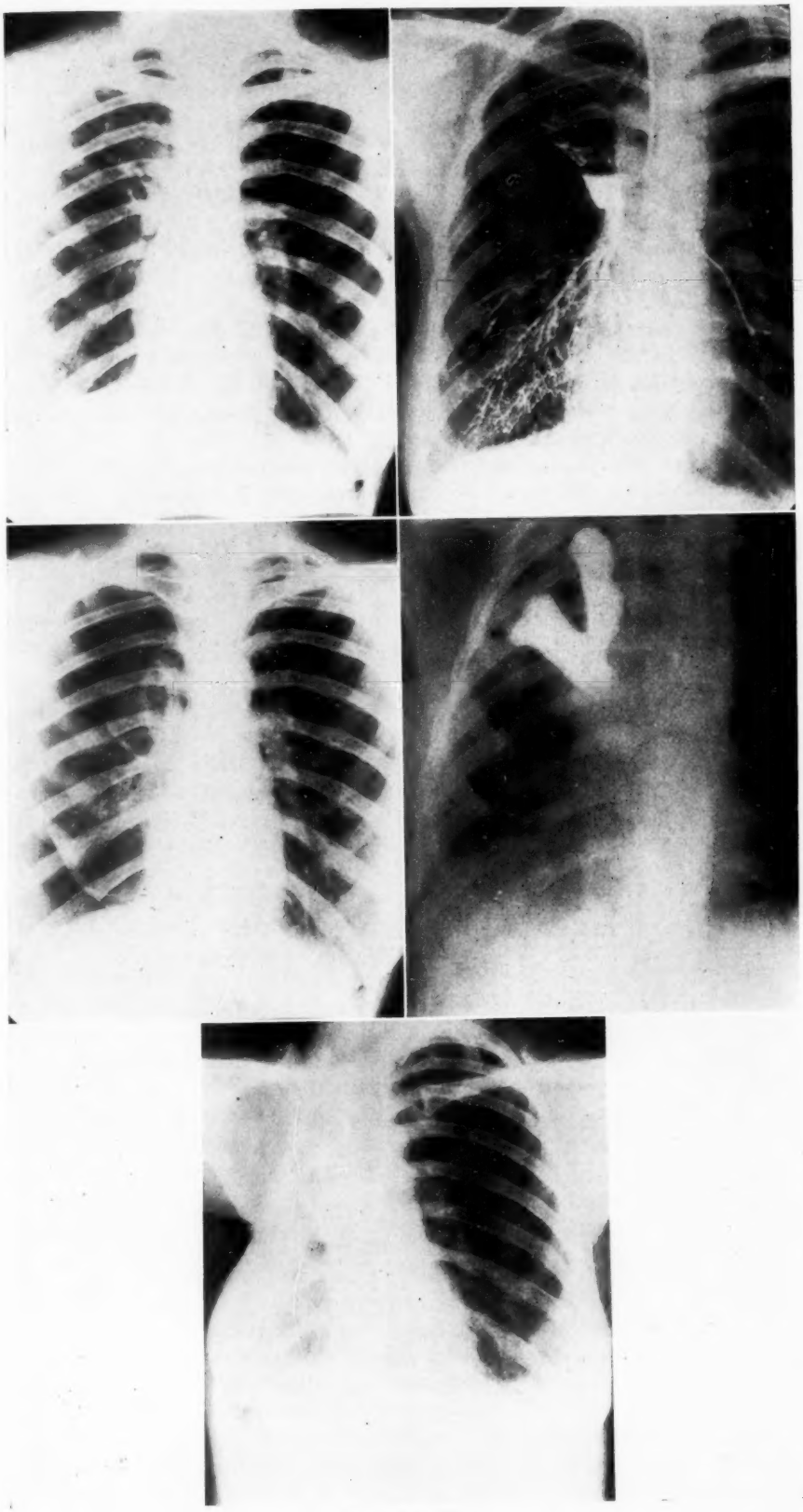
FIGS. 3A upper left, B upper right, C center left, D center right, E lower. Roentgenograms of patient W. S. with solitary cavity due to *Coccidioides immitis*. *A*, taken August 28, 1938, is the initial roentgenogram with thin-walled cavity in right upper lobe requiring lipiodol, *B* for clear delineation. *C*, taken March 28, 1940, after a year and a half of pneumothorax treatment, shows the cavity was still open. *D* shows the abscess cavity injected with lipiodol one year after lobectomy. *E* shows the collapse obtained by thoracoplasty.



FIGS. 3A–3E

thymol to the limit of her tolerance (between 2.0 and 3.0 g. per day) for a year when, experience with other patients having indicated its futility, thymol was discontinued.

She continued to receive pneumothorax from Doctor Randel at Fresno, and from Dr. Philip Pierson and his associates at Stanford, until March, 1940. Every three months she was hospitalized at Stanford for reëxamination. Whenever she had a cold, her sputum was examined and invariably yielded *Coccidioides immitis*. Roentgenograms revealed a well collapsed lung and the cavity was believed to have closed until lipiodol (figure 3C) demonstrated in March, 1940 that it was still fully open. From stomach washings, taken June 13, 1940, *Coccidioides immitis* was recovered. Believing that she was in constant danger of disseminating her infection throughout the rest of her body, we considered it advisable to remove her focus while she was still in good condition and, accordingly, lobectomy was advised.

Pneumothorax was discontinued in April, 1940, and the expansion of the lung was accompanied by pleural effusion. Pleural fluid removed March 23, 1940 contained no *Coccidioides immitis*. As the fluid absorbed, the pleural space was closed spontaneously by the requisite adhesions. She entered Lane-Stanford Hospital on July 17, 1940, for a right upper lobectomy. At this time her erythrocytes numbered 4,800,000; haemoglobin 85 per cent; leucocytes 15,000. Her vital capacity measured 2,400 cc. The sedimentation rate at this time was 20 mm. in the first hour (Cutler).

On July 20, 1940, under intratracheal cyclopropane anaesthesia, a semicircular incision was made following the breast fold under the right breast, which was then elevated, permitting entrance into the chest through the third interspace. The costochondral junctions of the third, fourth and fifth ribs were divided. The visceral pleura was everywhere thickened, white, shiny in appearance and adherent laterally as well as posteriorly where the indurated wall of the abscess was easily demonstrated, involving the midportion of the lung and firmly attached to the thoracic wall.

The hilar vessels to the upper lobe were isolated, individually ligated, followed by transfixion ligation and division of the bronchus. In the attempt to mobilize the lung posteriorly, the abscess was found to consist of an intrapulmonary part connecting with a localized empyema cavity. The wall of the abscess was completely excised and, in so doing, it was necessary to cut through the normal pulmonary tissue of the lower and middle lobes. The cut surfaces of the lung were closed with a continuous catgut stitch. The bronchial stump was covered with a pleural flap. Two mushroom catheters were introduced between the ribs for drainage and the anterior wound closed.

Following operation there developed an effusion in the pleural cavity and an abscess of the wound requiring reopening of the anterior incision. The pus obtained was cultured and found positive for *Coccidioides immitis*, *B. pyocyaneus*, *B. coli* and a diphtheroid. The bronchus reopened and a fistula into the wound was consistently demonstrable. The condition of the wound remained stationary for several weeks until sulfanilamide was blown into the wound daily with an atomizer. This did not control the coccidioidal infection but the prompt improvement suggested control of the secondary infection.

The persistence of the bronchial fistula and of a small empyema cavity in the area from which the lobe was removed (figure 3D) prompted readmission to the hospital in October, 1941, for a thoracoplasty, fifteen months after the lobectomy. The patient was in good general condition, with a vital capacity of 1,600 cc. and a haemoglobin of 69 per cent. The red cells numbered 4.4 million and the white cells 11,400. The sedimentation rate continued rapid (19 mm. in sixty minutes, Cutler method). At the operation on October 4, 1941, through a long paravertebral incision, practically the entire first rib was removed, together with half of the second, third, fourth, fifth and sixth ribs, and one-third of the seventh rib, thus permitting the scapula to fall into the wound.

The patient made an uneventful recovery and left the hospital on October 22, 1941, with evidence still of a small bronchial fistula. The wound has gradually diminished in size, accompanied by definite general improvement and an increase in weight. The sedimentation rate has steadily improved, being 10 mm. in sixty minutes (Cutler method) on February 6, 1942, four months after the thoracoplasty.

Comment: This patient reëmphasized many of the points previously mentioned as characteristic of coccidioidal infection. She, too, was a newcomer to the coccidioidal endemic area and, in the height of the dusty season, acquired her infection. Again, the infection was accompanied by the erythema nodosum, to which females are especially susceptible. Then she apparently recovered completely. However, one may suspect that even then she had developed the cavity, which is an occasional complication of coccidioidomycosis. Her haemoptysis in 1936 offered strong evidence of this mischief. In our other experience, in the case reported by Yegian and Kegel (9) and especially in Winn's extensive series (10), haemoptysis is the outstanding incident which results in the detection of these solitary cyst-like cavities. No roentgenogram was taken of our patient until an apparently entirely unrelated illness brought her to physicians who were alert to the implications of erythema nodosum in the San Joaquin Valley.

By analogy with reinfection type tuberculosis, some may feel certain that the cavity was produced by exogenous reinfection. While this is a possibility, we feel it is improbable. With the exception of her two attacks of "flu" early in 1938 (two years after her haemoptysis) she had no suggestive respiratory illnesses. Moreover, those two bouts of "flu" occurred in the winter when the chlamydospores of *Coccidioides* must be fewest in the air. Furthermore, with over 75 per cent of the population of the upper San Joaquin Valley infected within a ten year residence (11) the inevitability of reëxposure would be so great as to make these cavities of every-day roentgenographic occurrence, were they consequent to reinhalation of spores. We agree with Winn (10) that this type of lesion generally develops as a complication of the primary infection. A small excavation having occurred, either by the positive pressure balloon effect of the valve action in a bronchus or by a rent in the lung parenchyma, a large cavity appears. We (7) observed the development and the spontaneous closure of a cavity in a patient with a primary coccidioidal infection and Winn (10) has reported several who developed cavities and closed them successfully during their primary infection. On the other hand, Dr. Charles T. Kibler (12), of Tucson, Arizona, had a patient with a similar type coccidioidal cavity whose clinical story suggested that the cavity formation was delayed.

The small amount of "reaction" around the cavity, as seen by the cyst-like roentgenographic appearance and the histological examination of the specimen from our patient, would indicate that the infection was well arrested. The cavity would appear to have developed within the "focus" of the primary infection, the problem being that of a mechanical defect. As long as such a cavity persists, *Coccidiodides* would be present in the sputum. However, coccidioidal infections are not contagious, since the endosporulating spherules characteristic of coccidioides in man and other animals are poorly adapted to such ends

(1, 13). Hence the public health indication for closing these cavities in order to protect others does not exist. We appreciated this fact before attempting the lobectomy. Our reason for surgery was, as we mentioned, the fear that the patient was in danger of disseminating her infection throughout the rest of her body. However, even with the development of postlobectomy empyema and the resultant sinus tract with *Coccidioides* in its discharges and in the sputum, there were no peripheral coccidioidal lesions nor even extension to other portions of the lungs. The resistance to endogenous reinfection was amazing. It is important evidence for the theory (1, 13) that, once the primary infection has been "focalized" successfully, a high degree of immunity develops. Had the lesion not been located in such an unfortunate site, there is little doubt but that the patient would have been completely cured and her general health would have been benefited. However, this experience certainly reëmphasizes the importance of conservatism and the relatively slight risk of progression or dissemination which these lesions run.

J. W. F., a thirty-eight year old white American oil-driller, was referred to the Colfax School for the Tuberculous on April 4, 1939, by Dr. James F. Peattie, Chief Surgeon, Tide Water-Associated Oil Company, San Francisco, because of a cavity in the lung discovered one month previously.

In 1925 he worked for eleven months in the San Joaquin Valley and then moved to the coast of Ventura County. In 1931, while outside the known endemic *Coccidioides* area, he was in bed one month with pneumonia. In 1937 he returned to Kern County in the San Joaquin Valley. In May, 1938, he developed right-sided pleurisy with pain which he said was "behind the shoulder blade." A roentgenogram in June showed "a very faint shadow at the right top." However, he continued to work. In December he caught cold and raised clotted blood in morning sputum. There were no night sweats, no temperature above 99°F. and no weight loss. Since 1932 his weight had ranged from 140 to 145 pounds. Roentgenograms taken February 2 and 11, 1939 (figure 4A) revealed a cavity in the right upper lobe. This was suspected by Dr. Royal Hendricks, of the Foster Memorial Hospital at Ventura, as being coccidioidal in origin. However, an excellent roentgenologist reported that the film showed "rather extensive tuberculosis with cavity formation in the right upper lobe." Therefore, the patient was sent to the Colfax School for the Tuberculous for treatment.

Physical examination, on entry April 5, 1939, revealed a slightly thin middle aged white male who looked quite healthy. He was 67½ inches in height and weighed 140 pounds. His color was good; there was no cyanosis or curving of nails nor were the fingers clubbed. The only positive physical findings consisted of a few crepitations at the right base anteriorly.

Roentgenogram (figure 4A) showed "rather extensive fine mottling throughout the upper half of the right lung with a large cavity about 2 x 4 cm. in the right infraclavicular space. There was also some infiltration in the lower right lung. The hilar shadows were considerably increased and there was diffuse increase in the peribronchial markings throughout both lung fields. In the left infraclavicular space there was a considerable degree of scarring and some fine mottling in the first interspace."

Laboratory findings: April 15, 1939: haemoglobin 80 per cent; erythrocytes 5,460,000; leucocytes 11,100; polymorphonuclear neutrophils 61 per cent; large lymphocytes 11 per cent, small lymphocytes 28 per cent; no eosinophils. Erythrocyte sedimentation rate (Cutler method) 8 mm. in sixty minutes. Wassermann, negative.

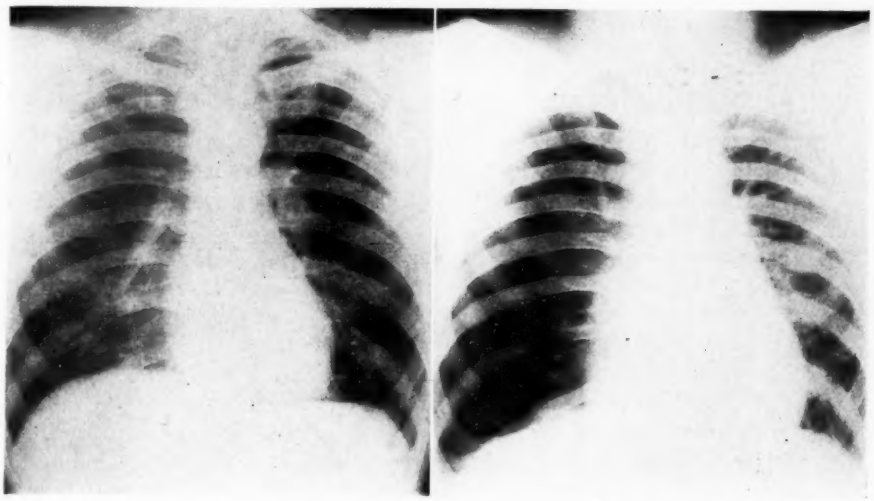
Examination of fifteen specimens of sputum, over a period of six months, failed to reveal tubercle bacilli.

Mantoux test on April 12 (1.0 mg. of OT) gave a four-plus reaction with severe constitutional symptoms.

Coccidioidin test June 2 (0.1 cc. of 1:1,000 coccidioidin intracutaneously) developed induration measuring 15 x 15 mm. with erythema and itching over an area 60 x 40 mm.

The diagnosis was finally established by recovery of *Coccidioides immitis* from the sputum as proven by guinea pig inoculation.

Pneumothorax was commenced on April 18 (two weeks after admission) and has been continued (figure 4B). Patient left the Colfax School for the Tuberculous on March 1, 1940, and returned to Ventura under the care of Doctor Hendricks. In October, 1940 (after eighteen months) Doctor Hendricks reported that roentgenograms showed that "the cavity, originally described in the right upper lobe, is no longer visible and both of



FIGS. 4A left and B right. Roentgenograms of patient J. W. F., with solitary cavity due to *Coccidioides immitis*. *A*, taken February 11, 1939, shows the thin walled cavity in right upper lobe. *B*, taken in February, 1940, shows a well compressed lung. In the original film there can be seen a small caviety which does not show in the reproduction. A film taken in October, 1940 showed the cavity entirely closed.

the lung fields are now free of evidence of recent inflammatory disease." Because of lack of experience regarding the fate of coccidioidal cavities when collapsed lungs reëxpand, Doctor Hendricks was requested to continue the pneumothorax refills.

Comment: As in our other patient with a solitary cavity, the lesion produced slight constitutional symptoms. The illness of May, 1938, occurring in Kern County and characterized by pleurisy in the right upper chest, strongly suggests primary coccidioidal infection. This possibility is further substantiated by the roentgenograms taken in June revealing a density in the right upper lobe. The cavity developed in this area, an association with primary infection discussed in the previous case. In the patient reported by Davis, Smith and Smith (7), the cavity which developed three weeks after the onset of symptoms closed spontaneously. It is to be recalled that their patient remained in bed, while

this present patient continued to work. It is certain that the cavity developed in the interval between June, 1938 and February, 1939. The haemoptysis occurring under the stress of coughing in November, 1938, like the interval haemoptysis in our other cavity patient, is a clue that a cavity had formed before roentgenograms established its presence. Again, it emphasizes the diagnostic importance of haemoptysis.

The successful closure of the cavity by pneumothorax has been very fortunate. Whether the cavity will stay closed when the lung is allowed to reëxpand, remains to be seen.

COCCIDIOIDAL GRANULOMA

The last two patients exemplify the coccidioidal granuloma discovered in North America by Rixford (14). This is the deadly disease which, fortunately, occurs only rarely as a complication of coccidioidal infection. The first case illustrates the spread of the fungus from the lungs and development of abscesses in bone and subcutaneous tissues.

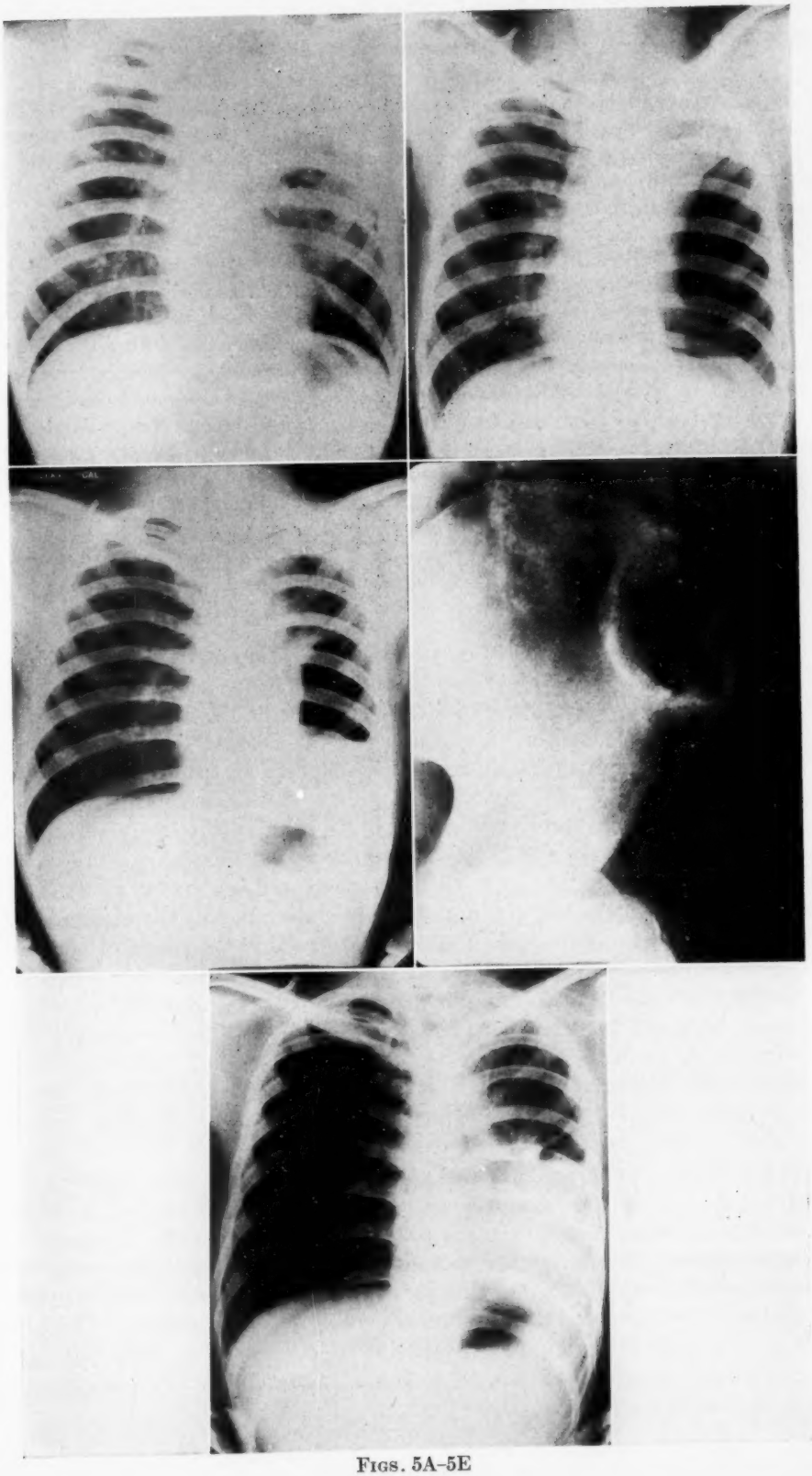
T. N., a twenty-year old American born Japanese houseboy, entered the Colfax School for the Tuberculous on October 18, 1939, with complaint of pain in the left chest and cough of ten days' duration. He was referred by Dr. Leslie Freudenthal, of Gridley, and Dr. M. A. Harada, of Sacramento, with a diagnosis of pulmonary tuberculosis.

Born in northern California, he was employed by a Marysville Hospital. Rarely had he been south of Marysville and only once had he been as far south as Sacramento. Not only had he never been in the San Joaquin Valley, but both he and his family declared he had never handled dried fruits, vegetables or vegetation from the San Joaquin Valley. His only past illness was a mild attack of influenza in 1937.

Previously in good health, on October 8, 1939, he experienced pain in the left chest accentuated by breathing. On October 11 he began to cough and, by October 15, was raising considerable sputum. At this time, fever and night sweats began and he tired very easily. He was seen by Doctor Freudenthal, of Gridley, and Doctors Harada and Orrin Cook, of Sacramento. A roentgenogram revealed extensive consolidation of the left upper lobe and it was diagnosed as acute tuberculosis. He was sent to Colfax.

Physical examination on entry revealed a moderately ill Japanese male of twenty. His temperature was 99.4°F. and pulse 94. Positive findings consisted of a friction rub over the lower third of the left chest anteriorly and posteriorly with râles heard anteriorly over the same region and above the clavicle. There were a few scattered crepitations above and below the right clavicle.

FIGS. 5A upper left, B upper right, C center left, D center right and E lower. Roentgenograms of coccidioidal granuloma, patient T. N. *A* reveals marked density of upper third of left lung with marked mottling extending below and involving the middle third of the lung. These findings were interpreted as involving both the pleura and the lung parenchyma and were at first believed to be tuberculous. *B* shows result of pneumothorax treatment. X-ray taken January 20, 1940 shows adherent apex and also small pleural effusion. *C*, taken May 17, 1940, shows apical density markedly cleared. Also shows much pleural fluid complicating pneumothorax. *D* shows the semi-lunar break in the contour of the right iliac crest illustrating the bed of the sequestrum which sloughed off as a result of coccidioidal granuloma of the anterior superior spine. *E*, taken August 28, 1940, shows marked improvement of apical pulmonary involvement and practical disappearance of density seen in 5B and 5C. Pleural fluid is still present.



FIGS. 5A–5E

Roentgenograms (figure 5A) revealed consolidation of the left upper lobe.

Laboratory findings: Haemoglobin 85 per cent; erythrocytes 5,270,000; leucocytes 14,900 with 78 per cent polymorphonuclear neutrophils, 9 per cent large lymphocytes and 13 per cent small lymphocytes. Erythrocyte sedimentation rate was 25 mm. in sixty minutes (Cutler method). Wassermann, negative.

Examination of ten specimens of sputum over a period of weeks failed to demonstrate tubercle bacilli. Mantoux test with 1.0 mg. of OT was negative. Coccidioidin test with 0.1 cc. of 1:100 coccidioidin was strongly positive. Guinea pig inoculation of pleural fluid obtained March 4, 1940 resulted in demonstration of *Coccidioides immitis*.

On October 20, two days after admission, left-sided pneumothorax was commenced. Adhesions prevented complete compression. Late in November the patient developed a pleural effusion from which the fungus was recovered. Within a few weeks he developed a large subcutaneous cold abscess in his left infrascapular and lumbar regions from which, following guinea pig inoculation, *Coccidioides* was recovered. The dissemination also involved the right anterior superior iliac spine, which sloughed off a sequestrum the size of a small walnut (figure 5D). There was, likewise, involvement of the right posterior cervical chain of lymph nodes with swelling followed by suppuration.

The patient was given intravenous injections of ball mill grind extract of *Coccidioides* in coccidioidin. There was definite clearing of the lung (figure 5E) and clinical improvement. However, in March, 1941 the patient was taken to Japan.

Comment: The period when this primary infection occurred cannot be stated. However, the infection is noteworthy, inasmuch as it was acquired in the Sacramento Valley, outside the recognized endemic area. The Sacramento and the San Joaquin Valleys together constitute the great Central Valley of California. The southern or San Joaquin half has been recognized as the outstanding area of coccidioidal infection. The historical position of dominance now appears to be menaced by Arizona, according to studies of Aronson, soon to be published, and of Emmons (15) and which amply substantiate the reports of Farness (16) Woolley (17) and Phillips (18). While central and southwestern Texas are also proven endemic areas, the San Joaquin Valley is still the most notable. Coccidioidal infections are most frequently observed in the southern portion of the San Joaquin Valley below Fresno. The northern region around Stockton has very few. Several cases of primary coccidioidal infection with erythema nodosum (in which the incubation period is definite (1)) have occurred in Yolo County in the southern portion of the Sacramento Valley. However, the infection in this Japanese patient was, in all probability, acquired in the vicinity of the mid-portion of the Sacramento Valley. The knowledge that infecting chlamydospores may be acquired from dusty products of the San Joaquin Valley, and even from contaminated clothing, minimizes any implication from this case that the fungus must necessarily flourish in the vicinity of Marysville. Moreover, an isolated case does not establish an endemic area. However, its recognition again emphasizes the necessity of keeping coccidioidomycosis in the differential diagnosis, even though a patient has had no known contact with a recognized endemic area. Either the region may be unrecognized or the mechanism of contact too devious to be apparent.

The clinical course in this patient is likewise noteworthy. The sudden onset

with severe pleural pain sounds very like a primary coccidioidal infection. One notes that here, too, we have a dark-skinned male. It is regrettable that roentgenograms were not available from the time of the onset of symptoms. The first roentgenogram, taken ten to fourteen days after his onset of symptoms, strikingly resembles that of our next patient, I. B., fourteen days after his onset (figure 6C). Possibly the prompt induction of pneumothorax assisted in the arresting of the pulmonary lesion.

The development of multiple abscesses, involving the posterior chain of cervical lymph nodes, subcutaneously on the back and the anterior superior spine of the right ilium, merely indicated the haematogenous dissemination of the fungus. These cold abscesses constitute the usual manifestation of coccidioidal granuloma.

The treatment with vaccine has been tried by various workers and with varying success. One apparent success was achieved by Templeton (19) by using vaccine prepared by K. F. Meyer. The results of Jacobson (20) are the most favorable reported. Results with vaccine which we have prepared and used or seen used have not been conclusive. Whether the material had any effect on the disease of T. N. is questionable. Certainly there had been no rapid, clear-cut gain. He seemed to be improving when his family insisted in taking him back to Japan but the improvement might have been transient.

I. B., the last case, is one of fulminating coccidioidal granuloma. For the information regarding it we are again indebted to the staff of the Tulare General Hospital. I. B., a thirty-five year old male Filipino, entered the Tulare General Hospital on September 22, 1940, with a complaint of fever and pain in the chest of four days' duration.

He had come to the mainland twenty years before but remained along the coast in Monterey County and did not come to the San Joaquin Valley and Tulare County until three years prior to his illness. He was doing field work near the town of Earlimart when, on September 18, 1940, he had a sudden onset of chills and fever, aching, cough and severe pain in the left chest accentuated by breathing. He grew progressively worse. On September 22 he came to the Tulare General Hospital and was admitted.

Physical examination showed an acutely ill, feverish Filipino male, coughing frequently and obviously in great distress. Physical examination of the chest failed to reveal any abnormalities. A presumptive diagnosis of pleurisy was made.

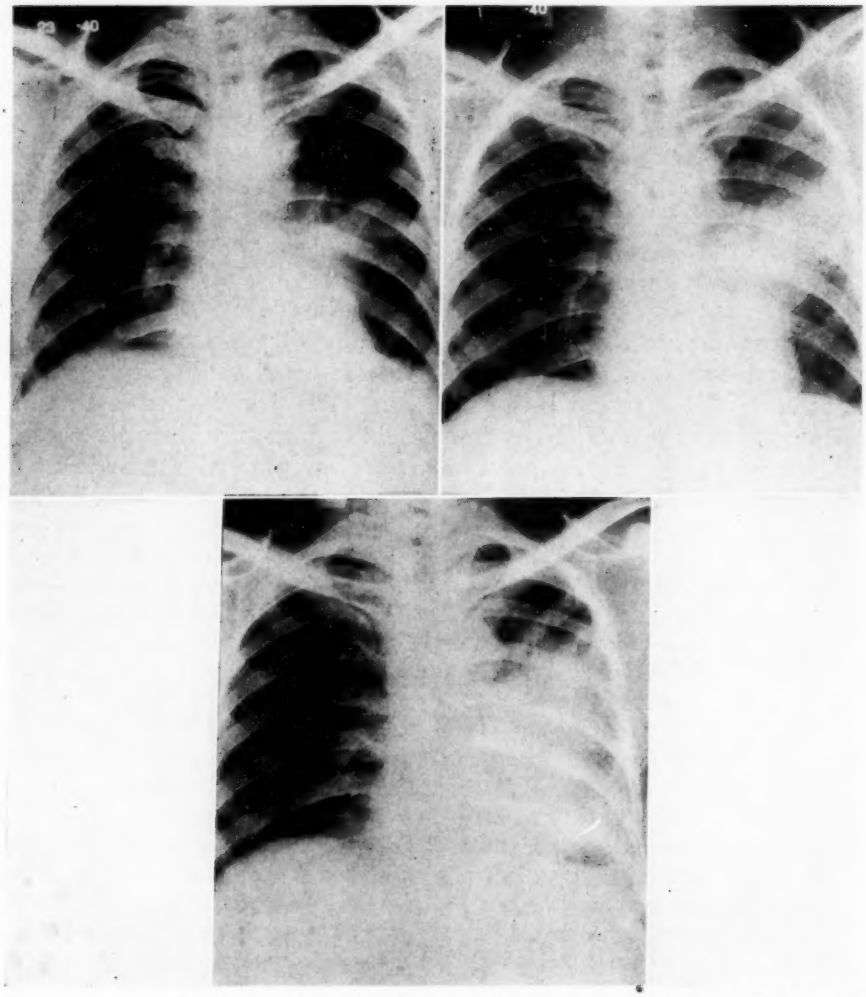
The roentgenogram (figure 6A), taken the day after admission (September 23) and only five days after his onset, revealed a wedge-shaped density extending from the left hilum to the periphery.

From a sputum specimen obtained September 26, 1940, *Coccidioides immitis* was recovered.

A roentgenogram (figure 6B) taken on October 1, only eight days after the first film, shows a considerable increase in the area of the density with smaller densities scattered throughout the left upper lobe.

Nine days later (October 10) and only twenty-three days after the onset of symptoms, a roentgenogram (figure 6C) demonstrated that practically the entire left lung was infiltrated and fluid was demonstrable. There appeared to be a haematogenous dissemination to the right lung. The patient's temperature ranged from 100° to 104°F. and he grew progressively worse.

Complement fixation test for coccidioidal infection on a specimen of blood obtained November 17, two months after his onset, revealed complete fixation through the sixth serial dilution (1:64) and practically complete fixation in the seventh (1:128). His



FIGS. 6A upper left, B upper right and C lower. Roentgenograms of coccidioidal granuloma, I. B. *A* was taken September 23, 1940, only five days after onset of symptoms. *B*, taken October 1, 1940, eight days later, shows rapid extension. *C*, taken October 10, 1940, nine days later, reveals extension throughout most of the left lung with fluid at the base.

serum showed four-plus precipitation through antigen dilution of 1:40, three-plus through 1:100 and one-plus at 1:200.

The patient signed himself out of the hospital and went to Monterey County. He returned to Tulare General Hospital on December 31, 1940, moribund, and died the same day, only three and one-half months after the onset of his illness.

Comment: The initial clinical picture (fever, malaise, cough and pleurisy) in C. Y. (the "San Joaquin fever" patient) and in I. B. are practically identical. The similarity of their first two roentgenograms (figure 1A and figure 6A) is apparent. Serological tests were not being performed when C. Y. was ill but the complement fixation of I. B. was characteristic of disseminated coccidioidal infection (coccidioidal granuloma), while his flaky precipitins were like those observed in recently acquired coccidioidal infections.

Elsewhere (13) the case of I. B. is being reported as an example of failure to focalize a primary coccidioidal infection. This dark-skinned male, who developed coccidioidal granuloma contrasts strikingly with the white female (C. Y.) who had erythema nodosum with her primary infection. They typify the relative susceptibility and resistance of these racial and sexual classes to which attention has been frequently called (1, 3, 8, 11, 20).

SUMMARY

By means of illustrative cases we have attempted to fill out our conception of what happens when man inhales chlamydospores of *Coccidioides immitis.*

The primary coccidioidomycosis which follows is an infection with all grades of severity. While it may be completely asymptomatic, there is often an influenzal-like illness marked by pleurisy. Frequently erythema nodosum also develops and occasionally a pleural effusion. Usually, as in primary tuberculosis, the infection is focalized.

Occasionally a pulmonary cavity develops, usually fairly soon after the primary infection. The cavity produces few symptoms other than an occasional haemoptysis which is not of sufficient severity to endanger life or even health. There seems to be little danger of dissemination from this lesion, even though the fungus may be present in the sputum.

Rarely, the fungus is not successfully walled off in the lungs and disseminates. Coccidioidal granuloma occurs as endogenous reinfection. The time of maximal danger is relatively soon after the infection is acquired. Every effort should be made toward safeguarding the individual at the time of his primary infection.

SUMARIO

Por medio de casos típicos, hemos tratado de completar nuestro concepto de lo que sucede cuando el hombre inhala los clamidosporos del *Coccidioides immitis.*

La coccidioidomicosis primaria que sobreviene es una infección que alcanza distintos grados de gravedad. Aunque puede ser absolutamente asintomática, toma a menudo la forma de una enfermedad influenzoidea caracterizada por pleuresía intensa. Frecuentemente también aparece eritema nudoso, y de cuando en cuando un derrame pleural. Por lo general, como sucede en la tuberculosis primaria, se focaliza la infección.

De cuando en cuando se presenta una caverna pulmonar, por lo general poco después de la infección primaria. Esa caverna provoca pocos síntomas aparte de alguna hemoptisis ocasional, que no alcanza suficiente intensidad para poner

en peligro la vida, y ni siquiera la salud. Parece que existe poco peligro de diseminación de esta lesión, aunque el hongo esté presente en el esputo.

Muy raramente el hongo no queda seguramente emparedado en los pulmones y se difunde. El granuloma coccidioideo se presenta como reinfección endógena, y la época de mayor peligro es relativamente poco después de contraerse la infección. Debe hacerse todo esfuerzo para salvaguardar al individuo cuando contrae su infección primaria.

Appreciation is expressed to the physicians who participated in the care of these patients, especially to the staff of the Tulare General Hospital and to Dr. Philip Pierson of San Francisco, California.

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ENLARGEMENT OF THE SUPERFICIAL LYMPH NODES IN BRUCELLA INFECTION[1]

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The recent paper of Wise and Poston (1), in which is reported the isolation of *Brucella* from the lymph nodes of Hodgkin's disease, has aroused new interest in the pathogenesis of this obscure disorder. Wise and Poston emphasize the fact that the lymph node lesions in their cases were typical of Hodgkin's disease, but they make no claim that the strains of *Brucella* which they isolated had any definite aetiological significance. Be this as it may, the clinical differentiation of brucellosis and Hodgkin's disease is not always easy: in both there may be prolonged fever of the undulating type, in both the spleen may be palpable and in both, at certain stages, the blood picture may show eosinophilia, leukopenia and lymphocytosis.

Inasmuch as superficial glandular enlargement is such a prominent feature of Hodgkin's disease, it seems important to know whether in true brucellosis one may encounter clinical enlargement of the lymph nodes. A survey of the standard articles on undulant fever yields conflicting statements, such as the following: "General lymph node swelling does not occur" (2); "Slight swelling of the lymphatics of the neck and groin sometimes occurs" (3); "Lymphadenopathy" mentioned among a long list of complaints and findings (4); "The submaxillary lymph glands are large and tender" (5). In a good many textbook articles no mention at all is made of the lymph nodes. General statements are also found in the periodical literature. Manson-Bahr and Willoughby (6) find that "There occurs a specific adenitis in this disease about the fourth month." Carpenter and Boak (7), in connection with their work on cultivation of *Brucella* from the tonsils, speak of large tender tonsillar lymph nodes, and Menefee and Poston (8) find that lymphadenitis is frequently present in brucellosis. Giordano and Sensenich (9) believe there is a glandular type of brucellosis in which regional nodes are affected by proximity to some point at which a large number of virulent organisms have gained entry. They report, for example, the case of a veterinary who had bouts of fever and enlarged axillary nodes after handling infected cows.

In view of all this confusion it seemed of interest to find out by a study of individual case reports the actual frequency of enlarged superficial lymph nodes in brucellosis. We were unable, curiously enough, to find any large series of detailed records, so that in the end it was necessary to turn to papers dealing for the most part with one or two cases. The references were taken from the Index Medicus, without any selection other than that they were in English, until we had encountered reports of 50 cases in which the condition of the lymph nodes was specifically mentioned. To achieve this end the somewhat tedious process

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of consulting 86 papers was necessary, as most of the writers did not mention the nodes at all.

The crude data for the study are summarized in table 1. It is immediately seen that lymph node enlargement is not uncommon. Even if one assumes that the nodes were not enlarged in all the cases in which no specific mention is made, one still finds adenopathy in 15.2 per cent of all cases; where the state of the nodes is noted, enlargement occurred in 58 per cent. However, inasmuch as the adenopathies in some of the patients (especially those of cervical nodes) may have been incidental and not a specific manifestation of brucellosis, it is necessary to consider the findings in individual cases (see tables 2 and 3).

A study of these tables shows deficiencies of the data which make interpretation of some of the cases difficult. There seems reasonable evidence for *Brucella* infection in nearly all, but the exact significance of the glandular enlargement is not always clear because of lack of full notes on the clinical course of the adenitis in relation to the progress and outcome of the disease, and because of lack of biopsies and cultures from the nodes. With the group of cases in which there

TABLE 1

Crude data for the study

Total case reports analyzed		191
No mention of lymph nodes		141
Stated that nodes were not enlarged		21
Nodes enlarged		29 } 50
Cervical nodes only	13	
General or other node enlargement	16	

Lymph nodes enlarged in 15.2 per cent of total cases.

Lymph nodes enlarged in 58.0 per cent of cases in which nodes are specifically mentioned (cervical 26 per cent, others 32 per cent).

was only cervical node enlargement it is particularly hard to be sure. Our impression is recorded in the table under the column headed "Remarks." But even after making these reservations it still seems established that in brucellosis enlargement of various superficial lymph nodes may occur as a specific manifestation of the disease, as, for example, in the cases of Severeide, of Williams and Shaw, of Leavell, Poston and Amoss, of Sharpe and of Menefee and Poston. We are unable, however, from this analysis to show clear relationships between glandular enlargement and the different varieties of *Bzucella*, nor is there convincing evidence of local regional adenitis in relation to the portal of entry of the organisms, except perhaps in the cases of Carpenter and Boak, of Williams and Shaw, of Giordano and Sensenich and of De Jong.

Another difficulty is the lack of adequate data on the pathology of brucellosis. Sprunt and McBryde (17) review the published fatal cases. With reference to the lymph nodes postmortem one finds such statements as the following: "The mesenteric nodes were often enlarged and many contained semi-fluid pulp from which *M. melitensis* was obtained;" "Microscopically, tubercle-like masses were observed in the spleen, lymph nodes and bone marrow;" "The lymph nodes were

swollen and contained masses of 'reticulocytes';" "The capsules of the lymph nodes around the hilus were infiltrated with lymphocytes. There were red cells as well as other cells in the sinuses of the nodes;" "Several lymph nodes showed reticulo-endothelial hyperplasia and phagocytosis of red cells." In Sprunt and McBryde's own case, "The peripheral sinuses of the lymph nodes from the hilus of the lungs and from mediastinum were filled with mononuclear cells. The lymph nodes of the mesentery presented a different picture, for there the lymph follicles were missing and the peripheral sinuses contained red cells many of which had been phagocytosed by macrophages. In some of the mesenteric nodes there was a slight increase in the amount of reticulum but this was not pronounced. The remainder of the node was infiltrated with mononuclear cells." Sprunt and McBryde feel that various types of cellular reaction may occur in response to *Brucella*. There may be reticulo-endothelial proliferations or infiltrations with lymphocytes and fibroblasts. In some cases the reaction may resemble tuberculosis and there may even be giant cells, but not of the typical Langhans type. There may be areas of focal necrosis. The lesions may resemble those seen in Hodgkin's disease at certain stages. Parsons and Poston (29) more recently discuss the subject. The description of the histology of the lymph nodes in their fatal case was as follows: "Grossly, definite large areas of necrosis could be seen. Microscopically, these areas were made up of homogeneous eosinophilic material containing very little or none of the original cellular element of the node. Around the edge of the necrotic areas could be found large pale cells with irregular pyknotic nuclei. These cells had the appearance of a remarkable reticulo-endothelial proliferation with considerable fibrous tissue replacement. In some areas very definite giant cells could be made out . . . There were numerous large cells indistinguishable from the Dorothy Reed type." Forbus in a discussion of this case summarizes his opinion by saying that there may be various types of cellular reaction to *Brucella* in lymph nodes, some of which resemble the lesions of Hodgkin's disease.

DISCUSSION

In summary, then, it appears that clinically noteworthy eniargement of superficial lymph nodes is not uncommon in *Brucella* infection. Just what percentage of these adenopathies are a specific manifestation of brucellosis—especially in the case of cervical lymph nodes—it is impossible to say from the available data, but in a number of instances the lesions appear to be specific. It will be important in future cases to describe in detail the course of the adenitis, to note whether glandular enlargement disappears as the *Brucella* infection clears up and to have more biopsies and cultures.

In certain cases, brucellosis can easily be confused with Hodgkin's disease. Prolonged undulating fever, palpable spleen, palpable lymph nodes and eosinophilia may be common to both and, as pointed out above, the cellular reaction in the lymph nodes of *Brucella* infection may on occasion resemble that seen in certain cases of Hodgkin's disease. Such diagnostic difficulty is illustrated by the following case.

TABLE 2

Cases with cervical lymph node enlargement only

AUTHOR	DESCRIPTION OF NODES	FURTHER DATA ON NODES: CLINICAL COURSE, BIOPSY, CULTURE	PROOF OF DIAGNOSIS OF BRUCELLOSIS	DATA ON SOURCE OF INFECTION	REMARKS
Habein (10)	"A few enlarged cervical lymph nodes"	None	Aggs. for *Br. abortus* and *B. melitensis* 1:320. Blood culture negative	History of ingestion of large quantities of raw milk	Possibly specific adenitis of brucellosis
Ross (11)	"Cervical adenitis"	Previous biopsy of a node showed "no tubercle or lymphadenoma"	Aggs. for *Br. abortus* 1:100	None	Significance doubtful
Kampmeier (12)	"Pea-sized lymph glands in cervical chain bilaterally"	None	Aggs. for *Br. melitensis* 1:320	A farmer. No definite source	Significance doubtful
	"Bilateral cervical lymphadenopathy"	None	*Br. melitensis* recovered from blood and urine. Aggs. 1:320	Italian schoolgirl drank goat's milk	Significance doubtful
	"Cervical glands were palpable"	None	*Br. melitensis* recovered from blood and urine	Patient used goat's milk	Significance doubtful
Murdock and Hall (13)	"Cervical glands slightly enlarged"	None	Aggs. for "alkaligenes melitensis" 1:300	None	Significance doubtful
Williams and Shaw (14)	"Cervical glands enlarged and tender without sore throat"	Autopsy. Positive culture for *Brucella var. abortus* from various organs. In the pathological diagnosis "acute lymphadenitis" is mentioned	Cultures postmortem	Patient drank large amounts of raw cow's milk	Probably specific adenitis of brucellosis

Baker (15)	"Several enlarged glands were felt in anterior and posterior triangles on both sides of neck"	None	*Br. melitensis* grown from joints	None	Significance uncertain
Wahl and Erickson (16)	"At onset there was slight enlargement of the cervical lymph nodes"	Nodes subsided in ten days	Blood culture positive for *Br. var. abortus*	None	Probably specific adenitis of brucellosis
Carpenter and Boak (7)	"The tonsillar lymph nodes in the neck were large and tender"	None	Aggs. for *Br. abortus* 1:5120. *Br. var. abortus* isolated from tonsils	Patient used moderate amounts of raw milk	Probably specific adenitis of brucellosis
Sprunt and McBryde (17)	"Cervical lymph nodes enlarged for 4 months before death"	At autopsy cervical and anterior mediastinal nodes enlarged. Lesions considered compatible with brucellosis			Probably specific adenitis of brucellosis
Chinn (18)	"Two moderately over-sized nodes in left anterior chain"	None	Aggs. for *Br. abortus* 1:640	None	Significance doubtful
Dever and Royce (19)	"A palpable lymph node at angle of right jaw"	None	Aggs. for *Br. abortus* 1:2560	Laborer in slaughter house	Significance doubtful

TABLE 3

Cases of lymph node enlargement other than cervical alone

AUTHOR	DESCRIPTION OF NODES	FURTHER DATA ON NODES: CLINICAL COURSE, BIOPSY, CULTURE	PROOF OF DIAGNOSIS OF BRUCELLOSIS	DATA ON SOURCE OF INFECTION	REMARKS
Kampmeier (12)	"Lymphadenopathy was present in the anterior and posterior cervical chains, axillary, epitrochlear and inguinal regions. The glands varied in size from a pea to small nut"	None	Aggs. for *Br. melitensis* 1:1280	None	Possibly specific adenitis of brucellosis
Herrmann and Edlund (20)	"Slight enlargement of the axillary nodes"	None	Aggs. for *Br. abortus* 1:1920	None	Possibly specific adenitis of brucellosis
Severeide (21)	"There were several palpable lymph nodes in each axilla, the largest the size of a hickory nut, firm, discrete. There were palpable pea-sized glands in each groin, also firm and discrete"	No note of course of the adenopathy, but biopsy showed "no Hodgkin's or leukemia"	Blood culture positive for *Br. var. abortus*	Patient was a farmer. No details as to milk supply, etc.	Probably specific adenitis of brucellosis
Williams and Shaw (14)	"The glands of the neck and groin swelled and were very tender." "Generalized lymphadenitis, the cervicals being more enlarged and tender than the others"	None	Three positive blood cultures. Aggs. for *Br. abortus* 1:1280	Patient drank large amounts of raw milk	Probably specific adenitis of brucellosis
Marietta (22)	"Slight generalized adenopathy"	None	Aggs. for *B. melitensis* 1:2000	None	Significance doubtful
Manson-Bahr and Willoughby (6)	Report enlargement of cervical and inguinal nodes in 3 cases but give no details	None		None	Significance doubtful
Wainwright (23)	"There was glandular enlargement"	None	Aggs. for *B. melitensis* 1:1280	None	Significance doubtful
Leavell, Poston and Amoss (24)	"The superficial lymph nodes were enlarged"	None	Aggs. for *Br. var. suis* 1:5120. *Br. var. suis* in stools	Worked in (pig) slaughter house	Possibly specific adenitis of brucellosis

Giordano and Sensenich (9)	"Recurring enlargement of axillary nodes and bouts of fever"		Positive skin test	Veterinary. Worked with infected cows	Possibly specific adenitis of brucellosis
Cruikshank (25)	"There was enlargement of the inguinal, axillary and cervical glands"	Gland enlargement "persisted until about the 5th week." Axillary gland biopsy-sterile showed "inflammation"	Aggs. for *Br. abortus* 1:2560	No data	Probably specific adenitis of brucellosis
Leavell, Poston and Amoss (26)	"Moderately enlarged lymph nodes were felt in the cervical, epitrochlear, axillary and inguinal regions, but only one right deep upper cervical node was tender"	None	Brucella, probably *var. suis* isolated from blood	Physician. Disease probably contracted in laboratory	Probably specific adenitis of brucellosis
Sharpe (27)	"There was a moderate generalized lymphadenopathy present especially of the axillary nodes"	Over a period of ten months of observation fever, arthritis, enlargement of spleen and lymph nodes persisted. No biopsy and no report on final outcome of case	Cultures of blood and synovial fluid negative, but positive agglutination tests in "high dilution" for *Br. melitensis*	No data	Probably specific adenitis of brucellosis
De Jong (28)	"There were large epitrochlear and axillary lymph nodes"	None	*Br. abortus* grown from spinal fluid. Aggs. for *Br. abortus* 1:320, *Br. suis* 1:220, *Br. melitensis* 1:20	Patient was a farmer. No definite history of infection	Probably specific adenitis of brucellosis
Menefee and Poston (8)	"Generalized enlargement of lymph nodes which were small, discrete and tender"	"Three days after entry lymph nodes and spleen decreased in size and all symptoms subsided." "Biopsy of supraclavicular nodes showed chronic lymphadenitis with necrotic foci. *Br. var. suis* was isolated from this node. "Multiple subsequent relapses but no further notes on nodes. Died of pneumonia. In the autopsy report is mentioned "lymphadenitis, non-specific." *Br. var. suis* recovered from lymph nodes as well as other situations. "Brucellosis with multiple small nodular lesions in lungs, liver, spleen, bone marrow and bronchial mediastinal, retroperitoneal, mesenteric, axillary and inguinal lymph nodes"		No data	Probably specific adenitis of brucellosis

CASE REPORT

H. M. (No. 201192), a forty-three year old butler, entered the hospital November 9, 1940, with the complaint of fever and painful joints. The past history was not remarkable; there was no story of exposure to any of the common sources of *Brucella* infection. Three weeks before entry the right shoulder became painful and this was soon followed by sore, swollen, red, hot knees and wrists. He had malaise, fever and night sweats. On entry he looked prostrated and there was still fever up to 38.5°C. The joints were clearing up. In both groins and axillae there were enlarged lymph nodes up to 2 cm. in diameter. The epitrochlear nodes were also readily palpable. The edge of the spleen was just felt. Physical examination was otherwise not remarkable.

A blood count on November 12, typical of the many blood studies that were made, showed: red cells 4.6 millions; haemoglobin 12.3 g. (Sahli); white cells 12,000; neutrophils 35 per cent (4,200); banded 16 and segmented 19 per cent; eosinophils 14 per cent (1,680); basophils 1 per cent (120); lymphocytes 49 per cent (4,880); monocytes 1 per cent (120); platelets 285,200; reticulocytes 0.8 per cent of erythrocytes. There were some smudged leucocytes but at no time on many counts were any atypical or primitive lymphocytes found. Urine and stool were not remarkable; Wassermann negative; sedimentation rate 32 mm.; blood urea 24 mg. per cent; uric acid 2.5 mg. per cent; tuberculin and coccidioidin skin tests negative; X-ray films showed lungs clear, heart and aorta not enlarged, no mediastinal mass, appearance of hand and shoulder normal. Agglutination tests gave the following results:

S. typhosus, *S. paratyphosus*, *A* and *B*	Negative
S. suipestifer	Negative
Sh. paradys, Flexner and Sonne	Negative
Br. abortus	1:80
Br. melitensis	1:40
Br. suis	Negative

The story of an acute febrile illness with arthritis, adenopathy and positive agglutination tests for *Brucella* suggested the diagnosis of brucellosis. This seemed confirmed by the brucellergen skin test which was strongly positive (0.1 cc. of 1:12,000 = erythema 4 cm. with induration 2 cm. in twenty-four to forty-eight hours). The blood count, also, while not typical is compatible with brucellosis, even the eosinophilia, according to the studies of Calder (30). On November 14 an axillary lymph node was removed for study. On section the normal architecture was represented by only scattered remnants of secondary follicles devoid of germinal centres. The bulk of the tissue was formed by masses of uniform small lymphocytes. There were a few scattered eosinophils. The appearance suggested lymphatic leukaemia to Doctor Wood and Doctor McNaught of the Department of Pathology. On November 27 another biopsy of a node from the groin showed the same changes. Cultures from the lymph nodes showed a few white staphylococci by routine methods. Special preparations under increased carbon dioxide tension yielded no growth. Numerous blood cultures were also negative.

The patient improved rapidly and within a few days after entry the inflammation of the joints had entirely subsided. Temperature after the first week remained normal and patient felt perfectly well. There was no notable change in lymph nodes or spleen and the blood counts continued about the same although the total white count on one occasion ran to 21,000 with 64 per cent lymphocytes. A bone marrow biopsy showed no abnormality.

The patient left the hospital on December 2, 1940, and has been followed to date (February 15, 1941) in the outpatient clinic. He has had no radiation therapy and aside from occasional aches in the joints feels well and is working. The lymph nodes and spleen remain unchanged and the last count showed white cells 18,700 with 59 per cent lymphocytes.

Discussion: There seems no doubt about a *Brucella* infection in this case. The point at issue is whether the adenitis could be interpreted as an atypical reaction to *Brucella* or whether the man had lymphoid leukaemia as well as brucellosis. Against leukaemia are the absence of any pathological lymphocytes, the eosinophilia, the normal bone marrow and the spontaneous improvement, although none of these rules leukaemia out.

The case illustrates very well the difficulty of differentiating brucellosis from "lymphoblastoma" and the perplexities which lymph node enlargement may create under such circumstances.[2]

CONCLUSIONS

1. Because of the possibility of confusing *Brucella* infection and Hodgkin's disease it is important to have accurate information about enlargement of superficial lymph nodes in the former.

2. In 50 unselected case reports of brucellosis in which the state of the lymph nodes is specifically mentioned, enlargement occurred in 29, or 58 per cent. In 26 per cent enlargement was confined to the cervical nodes and in 32 per cent other nodes were enlarged or there was generalized superficial lymphadenopathy.

3. In some of these cases the lymphadenitis is a specific manifestation of brucellosis, and if undulating fever and splenomegaly are also present, the condition can easily be confused with Hodgkin's disease.

CONCLUSIONES

1. Debido a la posibilidad de confundir la brucelosis y la enfermedad de Hodgkin, es importante contar con datos exactos acerca de la hiperplasia de los ganglios linfáticos superficiales en la primera.

2. En 50 historias clínicas de brucelosis tomadas al azar en que se menciona específicamente dicho estado linfático, observóse hiperplasia en 29 (58 por ciento): en 26 por ciento limitada a los ganglios cervicales, y en 32 por ciento afectando a otros ganglios, o tomando forma de linfadenopatía superficial generalizada.

3. En algunos de esos casos la linfadenitis constituye una manifestación específica de la brucelosis, y si existen simultáneamente fiebre ondulante y esplenomegalia, es fácil que esto acarree confusión con la enfermedad de Hodgkin.

[2] December 4, 1941, the patient is entirely well. Lymph nodes are no longer palpable. It is evident that he does not have leukaemia. Review of lymph node sections does not suggest infectious mononucleosis, nor were the lymphocytes suggestive. The heterophile antibody test was also negative. It seems probable therefore that the correct diagnosis was brucellosis.

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MILIARY DISEASES OF THE LUNGS[1]

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The term miliary was introduced originally into the language of pathology to designate certain minute foci of disease, generally numerous and disseminated widely in the tissues of the body. Although the presence of such foci in the lungs could be suspected during life, it could not be established clinically before the utilization of the X-ray and even then the cause of the shadows pictured remained to be demonstrated.

Our interest in the interpretation of such so-called miliary shadows was aroused in 1918 when the problem of a particular patient was presented. M. K., a youth of nineteen who had volunteered in the United States Army, contracted measles while on duty in France, and shortly thereafter had a frank haemoptysis followed by cough and the expectoration of tubercle bacilli in his sputum. Following the subsidence of the symptoms of clinically active tuberculosis, he was evacuated to the United States, where an X-ray film of his chest showed multiple so-called miliary shadows throughout both of his lungs. It was the subsequent disappearance of these shadows that raised the question as to whether the serial changes that were noted during a span of some months portrayed the complete healing of multiple tubercles or whether the shadows noted initially had been due to something else. Experimentally, Willis and I demonstrated in rabbits that we had viewed not true tubercles but minute areas of exudation caused by an allergic response of sensitized alveoli to the contact of tubercle bacilli or of tuberculin with them.

This experimental work established not only the hazard of too early or too dogmatic diagnostic and prognostic inferences from the viewing of what seemed to be evidence of a wide-spread seeding of the lungs with tubercles after an haemoptysis, but initiated a survey to record what conditions could give rise to similar roentgenographic changes.

A priori, they could be many and could be pictured in any state in which multiple, small areas of increased density develop in the pulmonary fields. Generically, they could occur whenever irritants—bacterial, viral, mycotic, chemical or neoplastic—find bronchial or pulmonary lodgment, whether by bronchial, vascular or lymphatic routes, or whenever disseminated pulmonary-vascular lesions, localized allergy or stasis in the lesser circulation occur. Specifically, therefore, these so-called miliary pulmonary shadows might be discoverable in various forms of sepsis, including tuberculosis, of generalized carcinomatosis or sarcomatosis, of aspiration of blood after an haemoptysis or after the inhalation of other foreign substances, of periarteritis nodosa, of congestive heart failure, etc. Though this was found to be true, it happened—and happens still—that the

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many possible causes of the roentgenographic changes are not borne in mind and but a few aetiological factors are considered when they are discovered.

The observations made over a period of twenty-three years supplemented by even cursory reading have disclosed some 22 states in which such miliary pulmonary shadows have been seen, to wit:

Tuberculosis
Pyaemia
Sarcoid
Carcinomatosis of bronchogenic or of extrapulmonary origin
Sarcomatosis
Bronchopneumonia
Atelectasis
Bronchiectasis
(Bronchiolectasis)
Congenital cystic disease of the lungs
Pneumonoconiosis (asbestosis)
Lipid pneumonia
Coccidiosis
Brucellosis
Tularaemia
Psittacosis
Leukaemia
Hodgkin's disease
Lupus erythematosus
Periarteritis nodosum
Xanthomatosis
Chronic passive congestion
Polycythaemia vera (Sossman)

In these many states, the symptoms were usually those of the primary pathological condition, the nature of which was indicated often by the history and by other accessory data. Localizing subjective manifestations were absent in most cases. Cough in some, thoracic discomfort or pain in others, haemoptysis without accompanying signs in a few were the more usual signalling symptoms. Usually, physical signs were lacking or meagre—most often these were showers of persistent, fine or medium moist râles elicited or increased by cough either with or without changes indicative of increased density of the lung. Not infrequently, the precise anatomical status of the lungs was not suspected prior to utilization of the X-ray. In the majority of cases, proof of the exact nature of the local pulmonary changes was lacking, consequently the proof of the aetiology of the lesions in many cases was presumptive and was based on the collation of all available clinical and laboratory data. Although, in most instances, the specific cause of the changes in the lungs can be inferred with reasonable accuracy, not infrequently it cannot be established without the demonstration of a particular pathogenic agent in the sputum or in the blood, by the utilization of other lab-

oratory procedures or even prior to direct anatomical investigation. It is to be emphasized, too, that the mere association of them with a systemic disease need not establish a unitary cause for the two as, for example, when the postmortem examination of a case of myeloid leukaemia showed that the pulmonary shadows were due to tubercles and that they were not caused by leukaemic infiltrations of the lungs. Finally, as a rule, it profits little to speculate whether the multiple pulmonary lesions resulted from a dissemination by vascular or by lymphatic channels or if they were spread by the bronchial route, unless the latter has been indicated clearly by the history of the case.

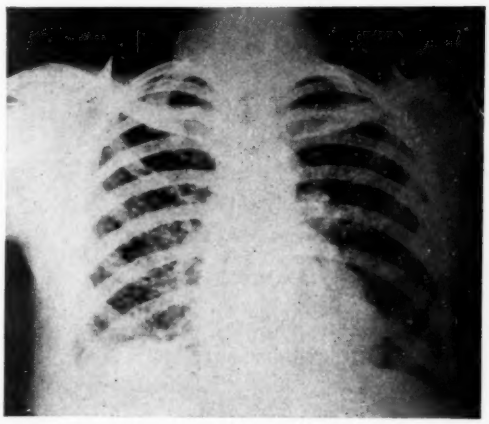


FIG. 1. Pulmonary miliary tuberculosis. M. B., a young Negro woman with generalized miliary tuberculosis. Tubercle bacilli demonstrated in the sputum.

Illustrative slides: The foregoing data are not new. Like those that King[2] reported to the American Climatological and Clinical Association in 1937, they are presented as a reminder and as an elaboration of facts already known.

So far as a cursory survey of the literature indicates, this report records a larger number of diseases in which so-called miliary seeding of the lungs may occur; it emphasizes particularly the hazards of drawing aetiological and prognostic inferences from roentgenographic shadows unsupported by all other available diagnostic data and points out that now and again proof of the true nature of the anatomical changes cannot be positive without direct inspection of the lesions.

[2] Donald S. King: Nontuberculous miliary lesions of the lungs, International Clinics, Vol. 1, Series 48, 1938.

FIG. 2. (upper left) Pneumonoconiosis. B. J. (219043), a white coal miner, age forty-two. Miliary pneumonoconiosis with emphysema. Dyspnoea, cough; no constitutional symptoms. No tubercle bacilli or fungi in sputum.

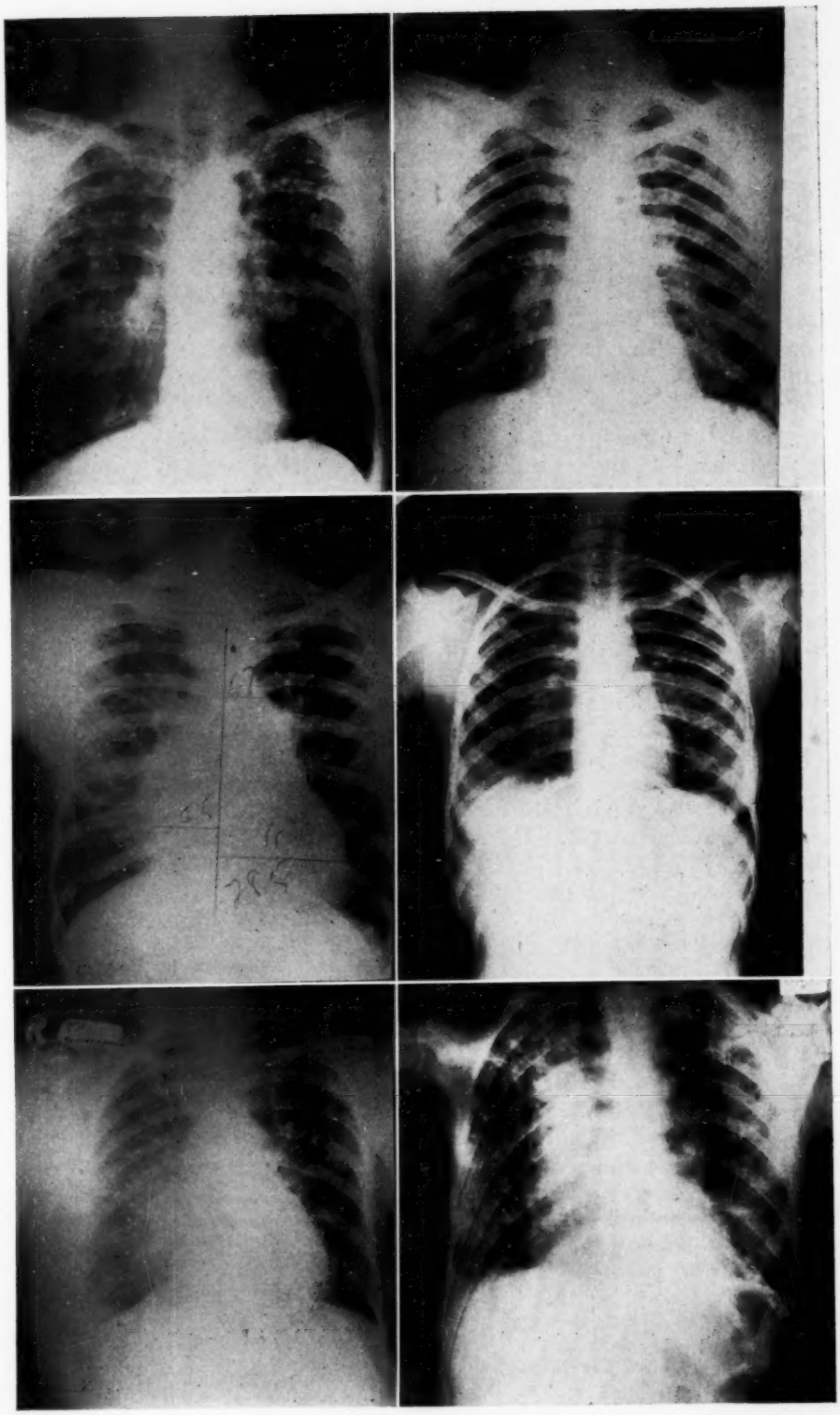
FIG. 3. (upper right) Miliary fibrosis of undetermined origin. H. H. (118936), a white man, age thirty-three, asymptomatic and without a history of exposure to abrasive dusts.

FIG. 4. (center left) Miliary shadows due to cardiac disease. S. P. (140505), a white man, age twenty-eight, with mitral stenosis and symptoms of myocardial weakness. "Miliary" shadows in midportion of lungs.

FIG. 5. (center right) Sarcoidosis. F. T. (156015), a Negro woman, age twenty-one, with enlarged peripheral lymph nodes, the biopsy of one of which showed typical lesions of sarcoid. No tubercle bacilli demonstrable. Negative intracutaneous response to tuberculin.

FIG. 6. (lower left) Miliary carcinomatosis of the lungs. A white woman, age fifty-six. Radical left mastectomy for adenocarcinoma. Miliary metastases to both lungs.

FIG. 7. (lower right) Cystic disease of the lungs. J. E., a white man, age fifty-seven, with a history of dyspnoea, loss of weight, weakness and a productive cough for three years. No tubercle bacilli demonstrated in numerous examinations of copious purulent sputum but structures diagnosed as fungi found in sputum led to diagnosis of "mycosis of lungs" in two clinics. Death was caused by coronary thrombosis and postmortem examination showed "cystic disease of the lungs with secondary inflammatory changes but no evidence of mycosis or of tuberculosis."



FIGS. 2–7

NONPATHOGENIC ACID-FAST BACILLI

EDWARD R. BALDWIN[1]

I. A Case of Chronic Pneumonitis Associated with a Nonpathogenic Acid-fast Bacillus

This interesting case was so unusual that it seemed to deserve a thorough study of the history and aetiology. It occurred in a mining town fifty miles east of Saranac Lake and the patient was under the care of Dr. T. J. Cummins, mining physician, who asked me to see her in July, 1932, and who kindly coöperated in this study. The patient was a young and very intelligent single woman of twenty-four, secretary in the office of the mine.

Owing to the unusual course of the illness her physician was puzzled and was unable to make a satisfactory diagnosis from physical, sputum and X-ray examinations. The following summary of the history gives the important features:

Miss I. P., age twenty-four, single, office secretary; parents living and well; family history negative for tuberculosis. Previous history was unimportant, except that she had severe pertussis in childhood with complete recovery. Her habits were excellent; she was under nervous strain from overwork in last two years. There was no exposure to mine dust.

Present illness: During the past year the patient lost weight and strength, which was attributable to overwork. She began to have difficulty in swallowing and regurgitated food frequently. Oesophageal spasm at cardiac end (achalasia) was diagnosed by X-ray. This was somewhat relieved by belladona. She had no cough or sputum. Fever gradually developed in the spring of 1932 accompanied by marked malnutrition and weakness. Four specimens of sputum were negative for tubercle bacilli at the State Laboratory. There was marked consolidation in the right lung from the second to the fifth rib level and a smaller area in the left mid-lung field, shown by X-ray and physical examination; there also was considerable dyspnoea and pallor. When seen on July 20, 1932, there was fever of 101° and 102°F., which had persisted for eight weeks at least. The cardiospasm (achalasia) persisted and sputum was always raised by vomiting. It was not foul-smelling and was only slight in amount.

The physical signs were characteristic of acute pneumonic tuberculosis, but the sputum being negative on repeated examinations aroused doubt in the mind of Doctor Cummins. I obtained a fresh specimen which was sedimented at the Saranac Laboratory. Smears were negative, but cultures on Petroff gentian-violet egg-plates gave two or three colonies of an acid-fast bacillus. These were isolated by Mr. Donald E. Cummings and put through a fairly complete bacteriological study. The cultures gave rapid growths on all the usual media for tubercle bacilli, and were rather creamy in gross appearance, resembling the avian type, but developing a salmon color in old cultures. Mr. Cummings was especially interested in identifying the organism because the patient worked in the office of a mine where silicosis was prevalent.

At first our theory was that the bacillus was an accidental contamination due to regurgitated food. However, the opportunity came to see the patient in September

[1] Saranac Lake, New York.

when she showed some improvement, though still very weak; fever of 100°F. persisted. The cardiospasm was present but was less marked.

Intracutaneous tuberculin tests were given consisting of 0.002 cc. of avian tuberculin on one arm and 0.001 cc. of human tuberculin on the other. Both resulted negatively. The anaemia and general condition may explain the anergy, as later tests were positive.

Meanwhile, four separate specimens of the vomited sputum were examined during three months and each revealed the acid-fast organism by culture only. Inoculations had been made by Mr. Cummings and Mr. Delahant of freshly isolated cultures without producing disease in guinea pigs, rabbits, chickens or white mice.

Further studies of the cultures convinced us that the bacillus was related to the timothy or grass bacillus group of acid-fasts.

The patient steadily improved during the winter of 1932–1933, gained 22 pounds and lost her fever. She was able to travel to the Trudeau Sanatorium for X-ray examination on April 22, 1933. Fluoroscopy of the oesophagus was confirmatory of the spasm, which continued but was less severe. The films (the first stereoscopically possible) revealed a probable cavity on the right side and some evidence of absorption of the pneumonic areas. There had been several slight haemoptyses since her improvement began.

She made another trip on May 31, 1933, when marked improvement was manifest in her nutrition and general appearance. There was little change in the chest signs and a little purulent sputum continued. On September 16, blood and sputum cultures were made, as well as intracutaneous tuberculin tests.

The sputum culture again showed growth of the same bacillus, but the blood was negative. The skin now gave reaction to Old Tuberculin 0.000,25 cc., but a stronger one to a tuberculin 0.001 cc. made from the acid-fast bacillus "P" itself, that is, an autogenous tuberculin. These tests were repeated on December 13, 1933, in comparison with timothy bacillus and human tuberculin, with reactions distinctly greater from the autogenous tuberculin and timothy tuberculin in doses of 0.001 cc. for each.[2] The patient now weighed 121 pounds, a gain of 35 pounds. The symptoms were very slight but occasional sputum was raised as usual, only by vomiting.

Altogether, six separate cultures of the same bacillus have been inoculated, a study of which was made by Doctor Petroff, Doctor Landau and Mr. Steenken (1) using the Petroff method of dissociation, and also by Dr. Arnold Branch (2) at the Harvard Pathological Laboratory, as well as by the late Dr. A. Stanley Griffith at Cambridge, England.[3]

The patient was presented to the Trudeau School class at Ray Brook in June, 1934, and in September she resumed full-time work. Signs of the consolidation on both sides were still present and cavity was suspected in the right lung in June, but except for an occasional blood-spitting and slight cardiospasm she was practically symptom-free.

Further history: In October, 1941, the patient was requested to appear for examination. She reported that she had continued at work for more than five years without interruption from illness. She had no symptoms except an occasional difficulty in swallowing, but

[2] The intracutaneous test was repeated in January, 1942, with the standard OT and autogenous OT, using the same dosage, namely, 0.001 cc. each, and avoiding areas of skin previously injected. The result was positive with the autogenous tuberculin, an area of 25 mm. wide being infiltrated after forty-eight hours. The standard Old Tuberculin, however, was entirely negative. To confirm the latter, the test was repeated two weeks later on the other arm with the same dose (0.001 cc.) and also gave a negative result. The loss of sensitiveness to standard OT seems unexplained since the acid-fast bacteria as a group cause some degree of cross sensitivity.

[3] No report was received of his observations.

no cough, bleeding or sputum. She was, however, short of breath when walking fast or climbing stairs. Her general appearance was good; her weight was 109 pounds; her highest was 121 in 1933.

Physical examination showed but little change in the signs in the chest. The area of dullness and harsh or bronchial breathing were somewhat less but there was, on percussion, some evidence of emphysema. There were no râles or ronchi but there was restricted movement of both sides.

X-ray films had been taken annually and showed little change from year to year. The following is the report of the reading made by Doctor Sampson of stereoscopic films taken October 22, 1941 by Doctor Cummins (figure 1):

"R. Residual fibrosis, result of previous infection, in the upper half. Compensatory emphysema in the upper third and also at the base.

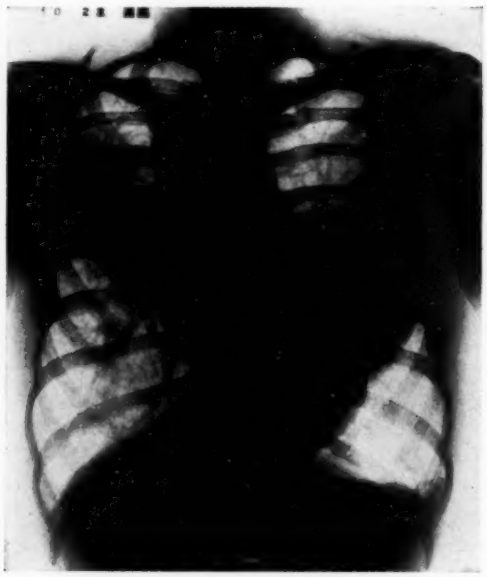


FIG. 1. I. P. X-ray film of lungs, October 22, 1941, showing dense induration on both sides

"L. Residual fibrosis, result of previous infection, in the middle third, with appreciable emphysema in the apex and particularly at the base.

"No signs of cavity in either lung, as previously suspected."

Discussion: The cause of the very acute pneumonitis in this case is possibly obscure, yet the question of the part played by the aspiration of food particles deserves attention. The coincidence of the publication of a similar case in the English journal Tubercle in November, 1933, is remarkable. Prof. S. Lyle Cummins, of Cardiff, Wales, described a woman who developed a pneumonia also associated with achalasia, whose sputum contained an acid-fast organism (3).

By exchange of cultures with Professor Cummins we found very similar characteristics possessed by them. The principal difference appeared to be in a mild pathogenicity for rabbits and white mice in Professor Cummins' culture "M" as compared with our culture "P". However, the suggestion may be made that the

small abscesses found in the lungs of rabbits and kidneys of the mice were obtained only with large doses of culture "M" and might be foreign body reactions.

The favorable course of the illness in the Welsh case was reported at the time, but we have no follow-up history.

In our case there was nothing to suggest lung abscess of the classic type, although the teeth were in bad condition. During the acute symptoms there was no chance for us to study the fresh sputum for spirochetes, but no other bacteria seemed to grow out of the sedimented sputum except air contaminants.

The question is pertinent whether the aspiration was the source of the pneumonia and the acid-fast bacillus a mere accidental accompaniment in both patients. Owing to the frequency with which green vegetable food must be contaminated with soil-bacteria of acid-fast, nonpathogenic types, it may not be surprising if these two unusual cases were so exceptional in atypical lung inflammations.

The question also arises whether such soil bacteria may not have become irritants to the lung in this patient when greatly debilitated due to vomiting and probable aspiration.

The fact that sputum examinations by ordinary smears on slides after sedimentation failed to reveal acid-fast organisms should make one cautious in excluding such organisms without attempts to cultivate them.

As was shown by Doctor Petroff (1), the "P" culture has the capacity to grow in a non-acid-fast form, acquiring acid-fastness quickly when nutritive conditions are favorable. The same property has been observed in some studies of soil bacteria by Hagen and his associates at Cornell (4), and in our own cultures from fruit and vegetable washings.

What is the prognosis of this patient and what will be the ultimate condition of the lung?

The fibrosis revealed by the signs and X-ray films seemed to the writer what in the usual terminology is called pulmonary induration.

After ten years one would expect the absorption of the disease area to have reached its maximum.

If this is correct, the development of emphysema and a permanent induration of the involved lung may be predicted. This seems at present consistent with a fair degree of health and a life of usefulness.

SUMMARY

A patient is reported who, following an episode of acute pneumonia and achalasia, developed fibrosis and emphysema. At repeated occasions a chromogenic acid-fast bacillus was isolated from her sputum. This bacillus proved not to be pathogenic for guinea pigs, rabbits, chickens and white mice.

SUMARIO

Tras un episodio de neumonía aguda y acalasia, una enferma manifestó fibrosis y enfisema, aislándosele repetidamente del esputo un bacilo ácidorresistente cromógeno. Este bacilo no resultó patógeno para cobayos, conejos, pollos y ratones blancos.

II. The Presence of Acid-fast Soil Bacteria on Raw Fruits and Vegetables

The history of the foregoing case suggested an examination of various foods eaten in the raw state, for the presence of acid-fast bacteria. It should cause no surprise that the latter are frequently present on fruits and vegetables grown in garden soil.

The studies of Frey and Hagen (4) at the Cornell Veterinary Laboratory, using special culture methods, showed these bacteria to be practically ubiquitous.

By direct smear it has been difficult to demonstrate them, doubtless because they pass through a non-acid-fast stage in growing and come to full development only under the most favorable conditions. These are furnished by the medium devised by Söhngen[4] and a comparatively high temperature, 45° to 50° C., which tend to suppress mold growths.

The following method was employed to collect washings of various fruits and vegetables:

> Sterilized tooth brushes (soaked in 10 per cent formalin, rinsed in boiling water) were used to brush the specimens after they had received the usual washing in the kitchen in preparation for table use. Sterile finger-bowls were used to collect the wash water, which consisted of 22.5 cc. sterile distilled water in each experiment. This was then pipetted by sterile pipettes into Erlenmeyer flasks containing a large parafined pebble and 22.5 cc. of Söhngen's medium. The medium was prepared in double strength, as it was diluted by equal parts of wash water, all being first sterilized in the autoclave. It was possible in most of the wash water to see particles of soil that had adhered to the vegetables and fruit which had been in contact with the garden soil.
>
> Fruits such as tomatoes, melons and strawberries, as well as windfall apples, pears, peaches, etc., usually produced some dirt in the scrubbing process.

After eight to thirty days, acid-fast rods in clumps of short bacilli were found in the scrapings from the pebble or from the paraffine pellicle near the pebbles, which were partly submerged. Many acid-fast cocci were seen which were identified as mold spores in most cases. Positive acid-fast bacillary growths were demonstrated in washings from lettuce, celery, carrots, onion sprouts, spinach, melons, tomatoes, strawberries, blue grapes, plums and blueberries. Negative smears were obtained from watercress, parsley, apples, pears, plums, cherries, white grapes and sweet corn. The tests were made between August 1 and September 25, 1932. They were continued between June 13 and October 13, 1933; again continued between August 21 and October 6, 1934.

It is possible that the results might depend on the season and soil temperature.

Cultures were also made from four samples of soil and one culture was isolated

[4] Söhngen's medium:

Potassium diphosphate	0.5 g.
Magnesium oxide or sulphate	0.2 g.
Ammonium chloride	0.5 g.
Water	1000 cc.

(Centralbl. f. Bakt. II, 1913, Bd. 37, p. 595)

by the plate method. No effort was made to obtain pure cultures from the washings. All acid-fasts demonstrated showed the quick growth, pigmentation, staining properties and morphology of *Bacillus phlei* (timothy grass). They were not tested for pathogenicity.

The fruits were obtained from markets and presumably they were not windfalls, but it is easily conceivable that the hands of the pickers were soiled.

The inference seems justified that acid-fast soil bacteria are so often eaten with food that cultures from the mouth or stomach contents might occasionally reveal them.

The bearing this might have on diagnosis is apparent.

Nonpathogenic acid-fasts have been demonstrated with considerable frequency in sputum, gastric washings, faeces, urine and from the tonsils, skin, etc. While there are minor differences described, they appear to be closely related. Possibly the reason that they are not found more frequently in sputum is that they are present in non-acid-fast stages of their growth-cycle.

SUMMARY

Chromogenic acid-fast bacilli, closely similar to *B. phlei*, have been isolated from various vegetables and fruits. The possible bearing of this finding on diagnosis is discussed.

SUMARIO

De varias hortalizas y frutas se han aislado bacilos ácidorresistentes cromógenos semejantes al *B. phlei*. En este trabajo discútese la posible relación de dicho hallazgo con el diagnóstico.

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CHRYSOTILE ASBESTOS AS AN INDICATOR OF SUBTILE DIFFERENCES IN ANIMAL TISSUES[1]

LEROY U. GARDNER

After fifty years of research the causes of natural resistance in different animal species and different organs to infection with the tubercle bacillus are still unknown. Chemical peculiarities of both invading organisms and of the host tissues have been assumed but actual knowledge of these peculiarities is limited. It has been shown that there are differences in the composition of human, bovine and avian type tubercle bacilli, but how they affect virulence remains to be demonstrated. Recent work on enzymatic activity in different tissues may lead to a better understanding of organ susceptibility, hitherto "explained" on hypothetical chemical, functional and morphological bases. The only suggestive bearing on species susceptibility that has been studied is that of body temperature and in this case the results have not been particularly promising.

In the course of investigating tissue responses to different kinds of mineral particles in a number of animal species, certain variations have been observed. The findings are presented and discussed not because they have any immediate bearing upon the problem of resistance to the tubercle bacillus but because they offer further proof of subtile differences in host tissues. No explanation for them has been discovered yet, but perhaps it may be easier to find one for pure mineral substances than for complex living agents like tubercle bacilli.

Most mineral particles of comparable small size provoke reactions limited to simple phagocytosis or relatively mild degrees of chronic inflammation. The response is similar regardless of host factors. Free silica in the forms of quartz, flint, etc. is a much more potent stimulus and it causes reactions similar to those excited by the tubercle bacillus (1). However, fine quartz particles are irritating under conditions not nearly as selective as those for tubercle bacilli. In the presence of water it has caused proliferation of connective tissue cells in any organ of any species of animal thus far investigated. The particles may be inhaled into the lungs in dry state or they may be injected in salt solution suspensions into other organs. Regardless of the pathway of introduction, amoeboid phagocytes and the lymphatic system ultimately insure the necessary contact between the irritant and connective tissue cells. Resultant stimulation produces a tubercle-like granuloma. Such reactions have been demonstrated in tadpoles, goldfish, domestic fowl, white mice and rats, guinea pigs, rabbits, cats, dogs, macacus monkeys and a baboon, and man of course responds in a similar manner. Any organ whose structure permits retention of adequate concentrations of fine quartz may be affected. By one or more methods, silicotic lesions have been produced in the lungs, pleura, spleen, liver, lymph nodes, bone marrow, subperitoneal and subcutaneous tissues, skin and brain (perivascular sheaths).

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

All of the minerals mentioned cause reactions so uniform in type that they have no significance for the question under discussion. There is one group, however, that does not conform to this rule; it exhibits specific variations in behavior when introduced into different organs of a number of animal species. These are the minerals generally known as asbestos. All of them are silicates consisting of combinations of various bases with hypothetical silicic acids. All are characterized by a fibrous structure due to peculiarities of molecular arrangement. Five different ones have been studied to some extent but this report deals only with one known as chrysotile, the common Canadian asbestos. This is a hydrated silicate of magnesium.

Asbestos not only possesses an unusual physical structure but it has special effects upon living animal tissues and is itself modified in a characteristic manner by contact with such tissues. In the lungs of human beings and in those of some, but not all animals, chrysotile produces the fibrous reaction known as asbestosis. After two or three months in such an environment the mineral fibres become coated with a mixture of albuminous substances and iron, forming the peculiar structures known as asbestosis bodies. In organs or tissues other than the lungs of all species that have been investigated, the injection of this mineral produces neither of these effects.

The asbestosis body is quite obviously a result of chemical reaction by host fluids upon the mineral fibre associated with a deposition of a coating substance. This coating is first laid down as a uniform layer along the sides of the asbestos fibre with swollen, club-shaped accumulations at each end. Shortly, perhaps because of cracks in the original smooth deposit, lateral buds develop at right angles to the fibre and as these buds increase in length their peripheral ends also become smooth and rounded. The resulting forms assume many bizarre shapes. Because of their high iron content, now proved to be derived from host sources, asbestosis bodies have the same bright yellow color as the blood pigment, haemosiderin.

The relationship between asbestosis body formation and tissue fibrosis is not the subject of this paper. Suffice it to state that evidence to be cited makes it appear that the development of these structures is incidental. Some, including the writer, are of the opinion that the mineral fibres cease to be irritating when the coating has been deposited upon them. The point under discussion is that chrysotile and other forms of asbestos behave differently in various tissues and hence can serve as an indicator of differences in host physiology.

Attempts to experiment with asbestos on the principles and with the same methods developed for quartz have resulted in many failures. On grinding these fibrous minerals to a very fine state of subdivision they do not become more irritating but practically lose all power to provoke tissue reaction. As analysis by X-ray diffraction reveals no change in molecular structure, one must assume that physical and not chemical alteration has taken place in the process of grinding. On the other hand, dehydration by heat changes both the chemical structure and alters the flexibility of the fibre so that it becomes very brittle. When chrysotile, thus treated, is injected into suitable locations it no longer

produces fibrosis nor are asbestosis bodies formed. The same is not true of quartz, which is still highly active after conversion to cristobalite or tridymite by heat treatment. It would therefore seem that a combination of physical and chemical factors is essential to the development of a typical tissue response to asbestos.

Table 1 summarizes various observations that have been made after introducing chrysotile asbestos into the *lungs* of different species of animals. As indicated, both inhalation of dry material and intratracheal injections of fluid suspensions have been employed. Since each method has produced similar results in two susceptible species, it seems probable that the choice of procedure has little influence on the outcome in the others. The only effect peculiar to the injection technique is the inflammatory reaction incident to the introduction of a large amount of material at one time. When this was deliberately done in some of the cats, the asbestos seemed to be dissolved very rapidly.

It will be noted that both the guinea pig and man develop fibrous reactions to asbestos and that asbestosis bodies form about the inhaled fibres. The cat,

TABLE 1

Pulmonary response of different species to chrysotile asbestos

SPECIES	ASBESTOSIS BODIES	FIBROSIS	OTHER REACTIONS	MAXIMUM OBSERVATION	METHOD OF INTRODUCTION
Man	++	+++	0	25 years ±	Inhalation
Guinea pig	+	++	−	33 months	Inhalation
		++		38 months	Intratracheal
Mouse	+	0	Phagocytosis	24 months	Inhalation
Cat	±	+	−	33 months	Inhalation
		+++	−	6 months	Intratracheal
Rabbit	±	+	Giant cells	41 months	Inhalation
Rat	0	++	−	25 months	Inhalation
Dog	0	0	Pneumonitis, granuloma	24 months	Intratracheal

rabbit and albino rat also react with characteristic tissue responses, but the rat's lung does not allow any asbestosis body formation; those of the cat and the rabbit permit it to only a limited degree. In our experience neither the white mouse nor the dog have exhibited any fibrous reaction although Schuster (2) has reported such changes in a dog that died after living ten years in an English asbestos fabricating plant. All our dogs, injected intratracheally with large amounts of long asbestos fibres in salt solution suspension, have shown only minute granulomata located in peripheral lymphoid tissues of the lungs. In these lesions there was no trace of asbestosis bodies or unaltered fibres. The reaction was fully developed one year after the injection, or perhaps earlier, and had undergone no further change during a subsequent year. The lung of the white mouse, on the other hand, readily formed asbestosis bodies but tissue response remained limited to phagocytosis by small mononuclear cells over a period of two years.

In *organs other than the lungs*, asbestos generally dissolves and bodies practically never develop regardless of the species of animal under investigation. On very rare occasions one or two have been detected in the peritoneal cavity and

subcutaneous tissue of guinea pigs injected locally with salt solution suspensions of the fibres. In man the so-called "asbestos corns," common on the hands of those who work with this mineral, consist of nonfibrous foci of chronic inflammation about an unaltered spicule of the mineral. The only other species in which chrysotile has been injected into extrapulmonary tissues have been rabbits and white rats. Here again neither bodies nor fibrosis have developed.

As further examples of the failure of tissues other than the lungs to react to chrysotile in a typical manner, one may mention the tracheobronchial lymph nodes and the pleura. Even in the presence of advanced disease within the lungs of man and susceptible animals, neither of these organs have shown asbestosis bodies. Their absence was formerly attributed by the writer to the inability of phagocytes to transport foreign particles of this shape and size through the lymphatic system. Recent experience with extremely short asbestos has demonstrated the fallacy of this inference. Typical bodies are formed in the lungs that are short enough to be entirely contained within a small mononuclear phagocyte and hence should be transported, but still none can be found in the tracheobronchial intrapulmonary lymphoid tissues. Similarly the fibrous pleuritis that invariably complicates a well developed asbestosis of the lungs is free of coated fibres. It is now assumed that preformed bodies may be carried to these locations but that they lose their coating material in the new environment.

Finally, petrographic study has demonstrated that asbestos fibres completely disappear within a few weeks after injection into any extrapulmonary tissue. Their solubility may be accelerated by inflammatory exudate. In the lungs of a moderately susceptible species, like the cat, for example, intratracheal injection of large amounts of long chrysotile fibres causes an acute exudative reaction in which the mineral seems to melt away within a week without suggestion of asbestosis body formation. Smaller numbers of fibres entering the lung by inhalation excite little inflammation. Under these circumstances they persist longer and about some of them a rather pale yellow coating develops. In the normal dog's lung the tissue environment is such that all injected chrysotile is dissolved within a year or, perhaps, less time, but if a main bronchus is stenosed so that collapse induration with venous stasis ensues, then solution seems to be somewhat retarded. Rows of yellowish globules, assumed to be the remains of fibres, are now visible.

All of these observations indicate that asbestos is a different kind of irritant from quartz, other minerals or tubercle bacilli. To produce the effects characteristic of asbestosis in the human lung a very particular environment is essential. The tissue fluids must be of such a character that the chrysotile fibres are not dissolved or coated with protective material too rapidly or too slowly. Within the limits of our observation, such conditions have been approximated only in the lungs of certain species. In the other organs of any animal neither fibrosis nor body formation occurs. It seems quite logical that the chemical environment in the lungs should differ from that of other organs in the same species. However, it is not generally appreciated that there are chemical differences within the lungs of such closely related species as the group of rodents included in this study.

All attempts to determine the particular factors in tissue environment responsible for this difference in behavior have been unavailing. Typical asbestosis bodies have not been reproduced *in vitro*. Those that have developed in living animals cannot be separated without some alteration of chemical structure and therefore their solubilities are difficult to establish. Further study of this highly selective irritant may yield information helpful in understanding why certain types of tubercle bacilli continue to proliferate in the tissues of some hosts and not in others.

SUMMARY

In the course of experiments upon the action of asbestos fibres upon living tissue it has been observed that this irritant is not like finely divided quartz, which provokes specific cellular responses in any organ of all species of animals investigated (tadpoles, fish, chickens, mice, rats, guinea pigs, rabbits, cats, dogs, monkeys and man). Asbestos fibres are acted upon to produce the "bodies," described by Cooke, only in the lungs of a few species like man, guinea pigs and white mice. They do not form in other organs of these species nor have they been observed in the lungs of white rats or dogs; in rabbits' and cats' lungs there are occasional atypical ones. Fibrous tissue reaction is also limited to the lungs, but none at all has developed in those of mice and dogs. The subtile differences in tissues responsible for such variation have not been identified but they may be of significance to the general problem of host resistance to other irritants like tubercle bacilli.

SUMARIO

En el transcurso de ciertos experimentos relativos a la acción de las fibras del amianto sobre el tejido vivo se ha observado que esta sustancia irritante no se parece al cuarzo finamente dividido, que provoca específicas reacciones celulares en cualquier órgano de todas las especies animales investigadas (renacuajos, peces, pollos, ratones, ratas, cobayos, conejos, gatos, perros, monos y el hombre). Las fibras del amianto son atacadas para producir los "cuerpos" descritos por Cooke, sólo en los pulmones de algunas especies, como el hombre, el cobayo y el ratón blanco, sin que se formen en otros órganos de estas especies, ni hayan sido observados en los pulmones de las ratas blancas o los perros, pero a veces se observan en forma atípica en los pulmones del conejo y el gato. La reacción fibrohistológica también se limita a los pulmones, pero no ha sido observada en los de los ratones y perros. No se han dilucidado las delicadas diferencias en los tejidos que ocasionan dicha variación, pero deben revestir importancia en el problema general de la resistencia del huésped a otros irritantes, como los bacilos tuberculosos.

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ABSTRACTS OF TUBERCULOSIS

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Tuberculosis and Mobilization.—Official regulations do not adequately provide for the exclusion of pulmonary tuberculosis from the United States Army. In spite of the remarkable decline in tuberculosis it still remains a serious menace particularly to persons of selective-service age group. The National Tuberculosis Association therefore recommends that orders come from Washington providing for X-ray study of all volunteers and prospective recruits and that induction be postponed until the results of the X-ray examinations are known.—*Tuberculosis and Mobilization, F. T. Lord, New England J. Med., June,* 1941, *224:* 971.—(S. T.)

Chest Examinations of Recruits.—The material used in the preparation of this paper was selected from approximately 10,000 roentgenograms of recruits from the southern half of the Province of Alberta, Canada, reviewed since the beginning of the present war. The recruit of doubtful chest fitness is examined by the clinician, and with his findings and the X-ray film as evidence, the clinician and radiologist weigh the results, and the recruit is classified into one of the following categories: fit for active service, fit for lines of communications, fit for services in Canada only, or, unfit for any service. The examination of the heart and great vessels is described with a view toward discovering congenital defects; hypertensive, arteriosclerotic and aneurysmal lesions; also rheumatic, syphilitic and thyrotoxic disabling conditions. In the examinations for diseases of the lung, advanced lung lesions were not considered, but great importance is attached to the minute active lesion and the so-called healed focus which require study. Recruits with chest shadows suggestive of low-grade infection, probably of upper respiratory origin, or with increased density in the peribronchial and perivascular tissues and also in the hilar regions, or with mottling in the parenchyma of the lungs, seem never to be entirely free from colds, but are always either just recovering from or developing a new cold. Men of this type are subject to breakdown and are considered as unfit, or fit for home service only, with the suggestion that they be reexamined in three to six months. In cases of healed minimal tuberculosis it is difficult to determine whether there is a focus in the lung not entirely healed which may be lighted up under service conditions. Such a lesion occuring within the past four years will rule a man unfit for any service. Cases of pulmonary fibrosis with evidence of sepsis are usually labelled unfit for service; others may be classified as fit for service in Canada. Chronic bronchitis with emphysema usually limits activity, it is aggravated by extremes in climate and renders the recruit unfit for military service. In healed cases of empyema,